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THE PROBLEM OF ALLERGIC CUTANEOUS VASCULITIS

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RECENT medical literature is resplendent with reports of clinicopathologic entities having, in common, reactions in and about the small blood vessels which are compatible with the phenomenon of sensitization. Morphologic changes in these entities vary from inflammation of the capillaries and arterioles of the proliferative or degenerative type, with fibrinoid degeneration or necrosis, to necrotizing angiitis wth characteristic granulomatous reactions. The clinical patterns range from rather benign focal reactions to disseminated fatal disease.

The entities may be separated into three groups, depending on the locus and severity of the vascular response, as predominantly dermal vasculitis, hypersensitivity angiitis, or necrotizing angiitis with granulomata. The skin and mucous membranes commonly are involved in the clinical course of these entities. Study of these easily accessible lesions often assumes diagnostic importance. We shall attempt to outline the entities within the three groups with emphasis on cutaneous manifestations and present two illustrative cases.

DERMAL VASCULITIS

Nodular Dermal Allergide.—Gougerot, in 1946,[12] proposed the name dermal allergide for a chronic recurrent illness characterized by joint pains and headache following which crops of localized skin lesions appeared suggestive of experimentally produced Sanarelli-Shwartzman reactions. The lesions appeared mainly on the buttocks and extremities in successive crops over a period of a week or more and persisted for a few

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weeks. The characteristic triad of lesions was erythemato-papular which at times became vesicular, purpuric, and dermal nodules. Occasionally wheals appeared or the nodules became necrotic. Histopathologic examination of the lesions showed a dermal inflammatory process, predominantly leucocytic, fibrinoid degeneration or necrosis of the collagen, increased vascularity, and inflammation of the capillary endothelium even to obliteration of the lumen.

About seventy cases have been reported since Gougerot's original observation, almost all from France. In most, the attacks had recurred over a period of years without impairment of health. There were no deaths reported. In about one-third of the reports, there was convincing evidence of hypersensitivity to drugs or microbial infections and hyperreactive responses to skin tests with bacterial allergens. Rarely, however, did elimination of drugs or antibacterial therapy influence the disease. Suppression of attacks by corticosteroids has been reported recently.

Allergic Cutaneous Vasculitis.—Ruiter, in 1952,[25] suggested the name "allergic cutaneous arteriolitis" to designate a clinicopathologic entity characterized by recurrent skin lesions, mild prodromal symptoms and a distinctive histopathology.

The clinical picture is apparently identical with that seen in dermal allergide, *i.e.*, polymorphic lesions, nodules, purpuric macules, erythema multiforme-like lesions and occasionally the other lesions previously noted. Histopathologically one observes changes quite similar to those observed by Gougerot, with but minor variations.[26]

Nearly all of the ten cases reported by Ruiter and others have either an allergic history or exhibit some definite allergic factor in their eruption. The course and prognosis of allergic cutaneous arteriolitis is apparently identical to that of nodular dermal allergide, although none of the cases has, as yet, been followed over an extended period. No systemic findings have been reported.

Dermatitis Nodularis Necrotica.—This rare cutaneous eruption first described by Werther in 1910[33] bears striking similarity to the previously described entities but appears to be a more severe example of the process. Polymorphic lesions of the type previously described appear in crops and are often ushered in by mild constitutional symptoms. They are dissimilar in that the nodules uniformly become necrotic. In addition there is a tendency to observe hemorrhagic bullae and plaques. The eruption tends to localize on the face, lower extremities, and buttocks but may be observed on any part of the integument.

In the early reports of cases the lesions were thought to be a peculiar form of tuberculide. Many recent cases have not been associated with tuberculosis and appear to fit well into the concept of allergic vasculitis.[1,5] Histopathologic examination reveals an embolic inflammatory process with

marked destructive changes in the small blood vessels leading to their obliteration. A perivascular reaction is observed and polymorphonuclear cells appear to predominate but lymphocytes and plasma cells may also be present. Some cases reportedly have been made much worse following skin testing with bacterial antigens. No effective treatment is available, although remissions have been produced with corticosteroids.

Pyoderma Gangrenosum.—Pyoderma gangrenosum is a rare affection of the skin characterized by distinctive ulcerations. The ulcers may appear rapidly or slowly and may begin as a sterile vesicle or pustule or merely an erythematous patch of skin. Occasionally polymorphic lesions resembling dermatitis herpetiformis are present.[2] Nearly all cases occur in debilitated adults, and are associated with chronic ulcerative colitis or occasionally with systemic infection. Histopathologic examination reveals a necrotic area beneath which there is marked vasculitis of the small vessels and a perivascular granulomatous reaction. Exacerbations have followed treatment with iodides. The Shwartzman phenomenon has been involved to explain pyoderma gangrenosum. Stoughton's[29] work demonstrating a proteolytic enzyme in the feces of patients suffering from ulcerative colitis may provide a clue to the etiology. No uniformly effective treatment is available, although gamma globulin (despite normal serum gamma globulin) has been said to be effective. Corticosteroids also appear to be effective, temporarily, in selected cases.

HYPERSENSITIVITY ANGIITIS

Hypersensitivity angiitis[15] is characterized by widespread fatal vasculitis produced by foreign serum or drugs. The onset usually follows the administration of the offending agent within a few days but may occur up to two weeks later. It is ushered in by malaise and fever and often an eruption. The process continues and there is gradual progression until prostration, cardiac or renal failure ensue. Death occurs in a few days to as long as one month after onset. Reported cutaneous lesions are non-specific and include erythema, urticaria, erythema multiforme-like eruptions, generalized hemorrhagic and purpuric eruptions, and eruptions suggesting dermatitis medicamentosa. Albuminuria, hematuria, leukocytosis, increased sedimentation rate and eventual increased blood urea nitrogen are consistent laboratory findings. A hemolytic anemia may occasionally occur. The following drugs have been reported to have caused this grave disease: sulfonamides (particularly sulfathiazole) thiouracil, thiourea, penicillin, organic arsenicals, diphenlyhydantoin (Dilantin®), aspirin, Lugol's iodine, streptomycin and (?) para-amino-salicyclic acid. Horse serum and in a few instances rabbit serum have often been experimentally used to produce a similar syndrome in animals and there have been a few serum-induced cases reported in humans.

Necropsy findings in cases of hypersensitivity angiitis reveal a marked

vasculitis of arterioles, venules, capillaries, and small arteries with a predilection for the renal and myocardial vessels but with lesions being very common in pulmonary and splenic follicular vessels. Nearly every organ in the body may reveal this profound vascular reaction with the exception of the gastro-intestinal tract and pancreas, which are usually spared. The viscera are edematous and microscopically one may observe a marked perivascular inflammatory reaction with evidence of fibrinoid degeneration of collagen. Thrombi of vessels may occur with resultant necrosis of grossly visible areas of tissue. Necrosis of the vessels themselves is constantly seen. Microscopically there is little evidence of a healing stage and it is striking that all lesions seem to be in the same stage of development. No granulomatous lesions are present. The kidneys often reveal a necrotizing glomerulo-nephritis.

There is little in the literature regarding the treatment of hypersensitivity angiitis. A report by Edge[6] (1955) mentions the so-called paradoxical effect of steroid therapy; dramatic improvement followed by sudden relapse and death. He attributed the unfortunate outcome in his patient to very rapid healing with fibrosis and subsequent vascular occlusion, bringing about vascular insufficiency.

NECROTIZING ANGIITIS WITH GRANULOMATA

Allergic Granulomatosis.—Churg and Strauss (1951)[4] defined a new entity, allergic granulomatosis, as distinct from classical periarteritis nodosa. The disease occurs in asthmatic patients and, according to one report, as a sequel of chronic ulcerative colitis. The syndrome consists of severe debility from the primary disease followed by intermittent episodes of fever, symptoms of vascular embarrassment in various organ systems, and eosinophilia. Cutaneous lesions occur in about two-thirds of cases and are of diagnostic importance, since their histology is compatible with the systemic process. Nodules are most commonly present and most characteristic. They tend to occur on the extensor surfaces of the arms and legs and on the scalp; lesions are also seen in other locations, particularly on the dorsa of the hands and the fingertips. The lesions are firm, usually non-tender, a few millimeters to a centimeter in size and are either flesh-colored, reddish, or purplish. Necrosis may occur and crusted nodules which eventually lead to scarring are seen. One also commonly observes urticarial, erythema multiforme-like and hemorrhagic lesions appearing in crops during the acute exacerbations of the disease. The histopathology of the nodular, necrotic and hemorrhagic lesions is usually characteristic of the general pathologic process, although this statement must be qualified by the paucity of biopsy specimens available.

Churg and Strauss[4] reported detailed autopsy studies of their cases and felt that the basic anatomical feature consisted of vascular lesions of the general type seen in periarteritis nodosa. The process involved most organ systems including the heart, lungs and spleen. Histopathologic examination

revealed fibrinoid degeneration, severe necrosis of small arterioles and venules, and granulomatous proliferation of epithelioid and giant cells. Serous membranes and extravascular connective tissue also revealed the reaction.

The prognosis is poor, although the disease may run a course of a few months to about five years. It is difficult to discuss treatment since the reported cases have all been from necropsy material.

Some authors consider this allergic granuloma of asthma to be similar to periarteritis nodosa except that the target organ is largely limited to a few segments of the vascular tree. In the involved segment, the lesions are still focal but involve all levels of the tree out to veins, and unlike classical periarteritis, the surrounding connective tissue shows intense fibrinoid necrosis. Like periarteritis, the noxious mechanism acts over only a very short period of time. The lesion is the natural homologue of the experimentally produced Arthus phenomenon, which is an exalted anaphylactoid reaction.

Lethal Midline Granuloma.—Two types have been proposed: the local (classical) type and the disseminate type. In the local type there is a chronic, destructive, granulomatous ulcerative involvement of the tissue of the upper respiratory tract. The disease usually presents chronic rhinitis with a certain amount of ulceration of the skin about the external nares. The sinuses and laryngeal mucosa may be similarly involved. The proliferative granulation tissue is resistant to most treatment and gradually spreads to cause extensive local destruction, saddle nose deformity, obstruction of the upper respiratory tract, and possible death by way of cachexia and malnutrition. Histopathologically, one observes a pronounced vasculitis, with thrombi, and a perivascular granulomatous reaction consisting of lymphocytes, plasma cells, giant cells and proliferation of small blood vessels.

Most recent authors compare the entity to Wegener's granulomatosis and its close counterparts and consider it an allergic vasculitis. The clinical course and pathology are certainly closely akin to Wegener's granulomatosis and would lead one to consider them variants of each other. Other authors, however, point out the occasional histopathologic similarity to neoplasm and feel that lethal midline granuloma is a variant of reticulum-cell sarcoma. Still a third group favor chronic bacterial infection as the most probable cause.

Friedmann[9] dissociates a disseminated form of lethal midline granuloma from the classical local form. The criteria for separation include evidence of vasculitis elsewhere and lack of external ulceration of the peri-nasal skin. He cites cases of local granulomatous rhinitis which subsequently revealed evidence of systemic vasculitis with terminal glomerulonephritis.

Cutaneous lesions associated with lethal midline granuloma include the localized ulceration of the facial tissues in the classic form and the re-

ported occurrence of nodules in the disseminated form. These nodules are identical to the nodules of Wegener's granulomatosis.

Wegener's Granulomatosis.—Wegener's granulomatosis is a rare entity having much in common with classical periarteritis nodosa but also representing striking clinical and histological variations for true periarteritis. The syndrome was first described by Klinger[14] in 1931 and formulated into a definite clinical entity by Wegener, in 1936. Fahey[7] and co-workers reviewed the subject in 1954 and documented twenty-five cases presenting the triad of pansinusitis, symptoms of arteritis and terminal renal insufficiency; the histopathological picture of a necrotizing vasculitis with granulomatous change.

The average case first presents persistent nasal discharge with severe sinusitis. Gross nasal hemorrhage is present at times. At about the same time one may note cough and occasional hemoptysis; the chest roentgenogram revealing a diffuse inflammatory reaction. The disease progresses and eventually signs of renal involvement are noted. Microscopic albuminuria and hematuria appear first but eventually nitrogen retention, evidence of glomerulitis and renal failure supervene. Death then follows. Other evidence of vasculitis may be apparent, skin being involved in approximately two of three cases.

Cutaneous lesions consist of nodules which appear in crops and tend to group themselves on the extensor aspects of the extremities, the volar aspects of the fingers, scalp and trunk. The nodules are firm, slightly tender, flesh-colored and vary from a few millimeters to about one centimeter in diameter. They may be slightly violaceous or erythematous and tend to have a slightly necrotic center with crusting at the summit. These nodules usually have the histopathologic appearance of the fundamental disease process, that is, necrotizing angiitis with granuloma formation. Petechial, hemorrhagic pustular and exanthematous lesions are occasionally present.

Necropsy findings in Wegener's granulomatosis have been extensively reported by Godman and Churg[10] and only the more important features will be considered in this paper. Practically every organ system is involved to a greater or lesser extent. The fundamental lesion is a necrotizing angiitis with a granulomatous reaction present in the perivascular tissue. The granulomas consist of polymorphonuclear cells, plasma cells, epithelial cells and eosinophils. Capillaries, small arterioles and venules reveal intimal proliferation and hyalinization of the walls with the occasional presence of thrombi. The entire process may be considered a necrotizing granuloma. A striking histopathologic feature is that one may see healing as well as active lesions, often they may occur side by side. This phenomenon points to a process that is characterized by remissions and exacerbations, an observation in accord with the clinical course.

Cortisone and its analogs have been used in the treatment of Wegener's

granulomatosis and in some cases have brought about temporary remission of the disease. A paradoxical steroid effect with rapid renal failure may occur. The prognosis in Wegener's granulomatosis is poor, most cases expiring in from one to five years. Cogan's Syndrome (granulomatous

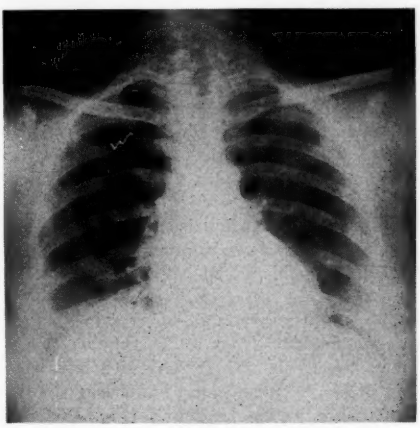

Fig. 1. Destruction of nasal bone and pansinusitis. Inflammatory infiltrates in lung (Case 1).

non-syphilitic interstitial keratitis) and idio-pneumonic granulomatosis have been considered clinical variants of Wegener's granulomatosis.[9]

Case 1.—*The patient was a white housewife, aged forty-six, with a history of persistent epistaxis, weakness and weight loss of one year duration. She had been in good health until March of 1955, when she first noted recurrent nasal obstruction and discharge, frequent epistaxis, persistent frontal headache, progressive loss of hearing and lassitude. At that time she gave a history of a normal roentgenogram of the chest one year ago, typhoid fever during World War II and a simple mastoidectomy twenty-five years ago (with slight residual hearing loss). In August of 1955, she was admitted to the Ear, Nose and Throat Service of the Presbyterian Hospital because of persistent fever and an increase in the severity of the above symptoms. Examination revealed a pansinusitis, more marked in the right maxillary antrum, which was corroborated on the x-ray films, and thickening of the tracheobronchial trees. Roentgen examination of the lungs (Fig. 1) showed a multiplicity of nodular densities consistent with inflammatory granulomatosis. Microscopic examination of curettings from the antrum showed a necrotizing granulomatous reaction, including occlusive fibrinoid degeneration of small vessels, consistent with a diagnosis of Wegener's granulomatosis. At this time there were no skin lesions; blood urea nitrogen was 12 mg per cent, E.S.R. 71 mm/hr and hemoglobin 12 gm. Urinalysis was normal. Numerous other laboratory tests were within normal limits. The diagnosis of early Wegener's Granulomatosis was made. In November the patient developed persistent inflammation of the left eye and was seen in the Eye Clinic where diagnoses of uveitis, episcleritis and iridocyclitis were made. She responded

*Patient presented before the Section of Dermatology, New York Academy of Medicine, May 1956.

fairly well to topical therapy but an unusual corneal opacity remained. The patient did relatively well until January of 1956, when she developed fever, hoarseness, cough, sore throat, marked weakness and anorexia. She also developed purpuric lesions of the palms, soles, thighs and hard palate. A week prior to admission she developed swelling of the ankles and marked shortness of breath. Laboratory findings on the second admission were as follows: erythrocyte sedimentation rate (E.S.R.) 130 mm/hr; hemoglobin 9.9 gm; Wassermann negative; serum gamma globulin increased; thymol turbidity ++; bromsulphalein (BSP) 15 per cent retention in forty-five minutes; urinalysis: albumin +++, numerous hyaline and granular casts, few white blood cells and many red blood cells, blood urea nitrogen 40 mg per cent. Chest roentgenogram revealed marked resolution of the previously recorded densities. Bleeding and clotting times were normal. Kveim Test (DM-1 antigen) negative. Old Tuberculin 1:1000 positive. Electrocardiogram negative. Urine, blood and sputum cultures negative. LE cell preparations negative. It was thought that the patient was entering into the angiitic and renal phases of her disease and she was placed on an initial dose of 70 mg of prednisone daily, with prompt lysis of fever, disappearance of purpura, improvement of urinary findings and general improvement. Despite this, blood urea nitrogen rose to 90 per cent. The steroid regimen was gradually increased to 500 mg daily with no change in the nitrogen retention. As prednisone was gradually lowered to 5 mg daily an erythematous eruption appeared on the face and trunk. This eruption cleared spontaneously in a few days. The patient continued to show subjective improvement and a moderate decrease in the blood urea nitrogen. Prior to discharge she developed a few small, non-tender, erythematous nodules on the elbows (Fig. 2) and a painful right index finger associated with bluish discoloration of the overlying skin. The eruption gradually faded and the patient felt fairly well at the time of discharge. In April of 1956, she developed a pustular and hemorrhagic eruption of the palms and soles and an increase in the number of nodular lesions over the elbows. Later, small nodules, in linear arrangement, appeared on the fingers (Fig. 2). The nodules on the fingers and elbows (Fig. 3) were bluish red, often with vesicular or hemorrhagic centers and tended to be in linear arrangement. Histologic examination of a nodular lesion on the elbow showed acanthosis of the epidermis with a necrotic crust. The cutis showed massive necrosis surrounded by a granulomatous infiltration as well as a more acute reaction consisting of polymorphonuclear leukocytes. Many vessels appeared to have undergone pronounced thickening of their walls; areas of fibrinoid degeneration being apparent. In the latter six months of 1956, the patient experienced exacerbations and remissions of her symptoms, fluctuation of the blood urea nitrogen and a waxing and waning of skin lesions. The symptoms gradually became more pronounced in early 1957, and she was re-admitted. Following several weeks of progressive renal and cardiac failure the patient expired in March, 1957.

The prominent findings at necropsy were destruction of the nasal bone and maxillary sinuses; acute periglomerulitis and obliterative glomerulitis with little normal renal tissue remaining; normal adrenal glands; arteritis with perivascular inflammatory reactions involving the kidney, spleen, sinuses, trachea, and lungs. The interpretation of the pathologist was that the histopathology was typical of neither polyarteritis nodosa nor Wegener's granulomatosis and was thought to represent the result of healing induced by prolonged corticosteroid therapy.

Case 2.—†The patient was a thirty-eight-year-old white, unmarried woman, employed as a cashier, first seen in 1953, with a history of recurrent skin eruptions for two years. She was in excellent general health except for gradually increasing colloid goiter since adolescence and outbreaks of hives or oral aphthae following the ingestion

†Presented before the Section of Dermatology, New York Academy of Medicine, October 1954, and the Atlantic Dermatology Society, March 1956.

of specific foods or aspirin. In 1951, she developed incapacitating stiffness and tenderness of the shoulders. Sodium salicylate was given by injection and almost immediately an alarming generalized edema developed which was followed by urticaria for a week. Shortly thereafter, the present attacks began. They are characterized by migratory pain in the shoulders, arms and legs; headache, fever and

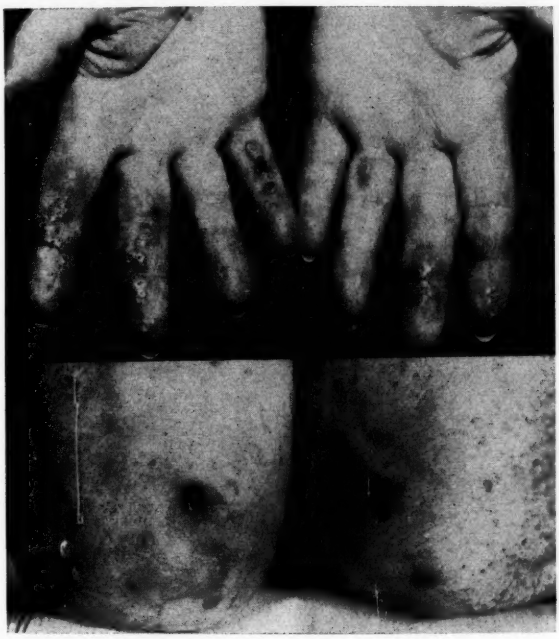

Fig. 2. *(Above)* Nodular necrotic and non-necrotic lesions on fingers (Case 1).
Fig. 3. *(Below)* Nodular necrotic lesions on elbows (Case 1).

fatigue, stiffness of the hands, and then the sudden appearance of polymorphous localized skin lesions. New lesions appear for a week, resolve slowly and when they are almost healed another attack occurs. In 1952, the patient noted occasional epistaxis followed by dryness of the nasal membranes and a painless hump in the middle of her nose. During one of the attacks she took a proprietary medicine containing 10 grains of aspirin and within a few minutes lost consciousness and was rushed to a hospital where she remained for two months. A diagnosis of subarachnoid hemorrhage was made after neurologic, x-ray and spinal fluid examination. A chest x-ray was normal as was the urinalysis. The skin lesions disappeared while on large doses of Benadryl® but reappeared when it was discontinued because of retention of urine.

When the patient first came under our observation in 1953, skin lesions had been persisting for two months. On examination, the skin was pale and there were a few wheals scattered over the face and trunk. The patient attributed these to having eaten cucumbers which she knew had caused hives previously. There was an atrophic depressed scar across the nose (Fig. 4). A small symptomless indolent ulcer was present in the base of the tongue. There was a diffuse prominent enlarge-

ment of the thyroid. The lesions for which the patient sought relief were confined to the extremities and buttocks. The latter were covered with erythematous vesicles in various stages of evolution. A few were hemorrhagic. There were scattered painful hemorrhagic vesicles on the palms (Fig. 5) and erythematous papules about the knuckles. In linear arrangement, above, and below the elbows were erythematous

Fig. 4. Saddle nose deformity (Case 2).

areas in which there were papules and nodules, some having centers covered with hemorrhagic crusts (Fig. 6). Scattered on the legs and ankles was a polymorphous eruption consisting of erythematous macules, vesicles and purpuric spots. There were no abnormalities of the joints. The heart, lungs and abdomen as well as the blood pressure were normal. On examination, the urine, white cell, and platelet count, bleeding and clotting time and metabolic rate findings were normal. There was a secondary anemia (hemoglobin 7.8 gms) and slight elevation of the sedimentation rate (38 mm/hr). Histologic examination of a nodule excised from the elbow showed an intense predominently polymorphonuclear infiltration in the corium and upper subcutaneous level with edema and necrosis of collagen, increased vascularity and swelling of proliferating endothelial cells. A small sub-epidermal edematous bleb had been formed. No bacteria could be stained. The examination of a biopsy from the tongue ulcer showed a non-specific congested inflammatory ulcer without necrosis of the vessels. Special examination of the nose and throat revealed only atrophic rhinitis. X-ray of the sinuses were normal and the nasal bones were intact. The defect in the profile (inward displacement of the soft tissues of the nose on the lateral view) was due to collapse of the cartilaginous structures inferior to the nasal bone. The diagnosis of nodular dermal allergide was made and for eight months various regimes were carried out. These consisted of ferrous sulfate and high protein diet, trials with elimination diets, search for focal infection, change of environment, antihistaminic and antibiotic therapy, isoniazid, cholorquin, phosphate, potassium iodide and finally, small doses of corticosteroid drugs. Ferrous sulfate soon restored the hemoglobin to normal. Isoniazid caused violent attacks of sneezing,

potassium iodide was followed by swelling of the neck and an exacerbation of skin lesions, cortisone depressed the symptoms temporarily.

During a severe exacerbation in 1954, requiring admission to the hospital, x-ray examination of the chest showed a diffuse, fine, interstitial infiltration throughout both lung fields, more marked at the bases which was consistent with the diagnosis

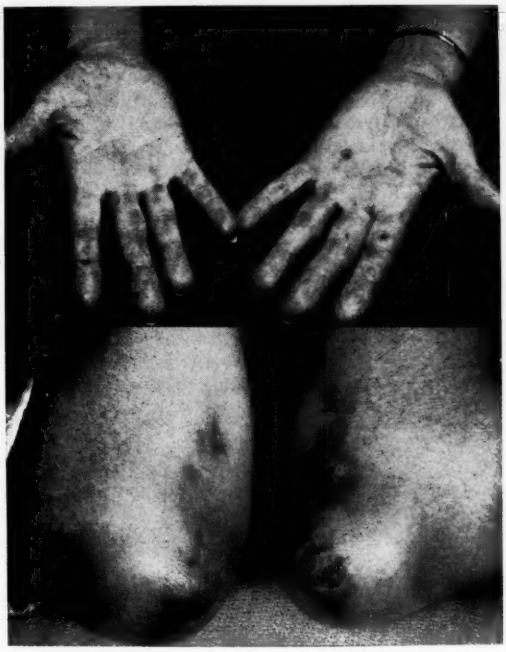

Fig. 5. *(Above)* Scattered hemorrhagic vesicles, hemorrhagic and non-hemorrhagic papules on the fingers (Case 2).

Fig. 6. *(Below)* Symmetrical erythematous papular and nodular lesions about elbows. Central hemorrhagic necrosis in some of the nodules (Case 2).

of allergic angiitis. Extensive chemical, serologic and bacteriologic examinations were unrewarding. On skin testing with fungus and bacterial antigens, including tuberculin, there were negative findings. Suppressive doses of corticotropin produced resolution of all symptoms.

For the next thirty months, 50 to 200 mg of cortisone, daily, sufficiently controlled the attacks to permit the patient to work except for a short interval in 1956, when nodules and hemorrhagic blisters on the legs became deeply necrotic. Because of the increasing goiter and dysphagia, endocrinologic consultation was obtained in June of 1957. The basal metabolic rate was plus 25 and protein bound iodine slightly below normal (5.1 mg per cent). Tri-iodothyronine (Cytomel®) 25 mcg daily was administered and within five days the patient developed fever, arthralgia and a shower of new lesions which were not controlled by stopping the Cytomel® or increasing the dose of cortisone.

On admission to the hospital for the second time in November 1957, the general

examination was the same as on the previous admission except that the lesions on the legs had again ulcerated and the goiter had increased. Examinations made by the ear, nose and throat department were of special interest. The nasal mucosa was atrophic and under the saddle nose deformity the mucosa was covered with oozing crusts. A biopsy showed the same morphology as did the previous ulcer of the tongue, a congested, inflammatory ulceration. X-ray examination of the esophagus following Lipiodol® and barium swallow showed two large radiolucencies impinging on the posterior wall in front of the cervical vertebrae. These were interpreted as thyroid or granulomatous masses. Laryngoscopic examination was normal except for the masses in the hypopharynx. Biopsy of one of these polypoid masses showed a somewhat hypertrophic squamous epithelium and in the subepithelial tissues there was marked capillary proliferation and focal paricapillary accumulations of mononuclear cells in granulomatoid clusters. No organisms were visible. Patch tests were done with drugs the patient had taken as well as with controls. There was a slight reaction to quinidine and to sodium salicylate. At the site where 25 per cent potassium iodide in vaseline had been applied a marked acute vesicular hemorrhagic dermatitis developed. This lesion, an early erythematous vesicle, and an indolent nodule were strikingly similar on morphologic examination varying only in intensity of cellular reaction. There was the same inflammatory reaction, necrosis of collagen, congestion and endothelial swelling of the capillaries as seen in the nodule excised four years previously. Repetition of laboratory tests including serum cholesterol, serologic tests for syphilis, were the same as previously noted except the electrophoretic partition of serium proteins showed a lowering of the albumin (2.9 gms per cent).

Therapy was the same as on the previous admission with the addition of a low iodine diet. The lesions gradually resolved but later iodine had to be reintroduced due to signs of hyperthyroidism. At present new skin lesions of moderate severity continue to appear but the patient is able to work while taking from 50 to 150 mg of cortisone daily.

DISCUSSION

The broad concept of allergy as expressed by von Pirquet has made it possible to study different diseases and diverse manifestations from a common viewpoint. This concept of the altered capacity to react which an organism achieves after acquaintance with organic or inorganic substances is well accepted.

In the entities described, specific allergic reactions would include hypersensitivity angiitis and allergic granulomatosis associated with asthma. In the group of dermal vasculitis and in necrotizing angiitis with granulomata, the cause and effect relationships do not seem to be convincingly established nor has specific sensitization been proven. However, it is commonly accepted that hypersensitivity, allergic or pathergic, may cause inflammatory, proliferative, or degenerative changes in and about the small blood vessels. Lesions, identical to those described, have occurred in patients specifically sensitized to chemicals, foreign sera or microbes. With the exception of Wegener's granulomatosis many of the case reports strongly suggest that sensitization to organic or inorganic substances, in predisposed individuals served to set off these peculiar clinical patterns. Drugs appeared to initiate the symptoms of hypersensitivity angiitis and to produce an exacerbation or a recurrence in dermal vasculitis and in

allergic granulomatosis. Many different drugs have been implicated, more particularly iodides, sulfonamides, and thiourea compounds.

The records suggest that sensitization to bacteria from focal or systemic infections initiates or causes exacerbations or recurrences of dermal vasculitis. It is possible that the midline granuloma and allergic granulomatosis associated with asthma are influenced by sensitization to bacteria found in the respiratory tract. However, elimination or suppression of substances thought to initiate or intensify these various diseases rarely effects a cure. There are an increasing number of reports on their suppression, at least temporarily, with the administration of corticosteroids. Again this response suggests that allergy is, at least, in part responsible for the various diseases.

Several authors have suggested the similarity between the inflammatory vascular reactions seen in the various diseases and the experimentally induced Sanarelli-Shwartzman phenomenon. Using this concept it is easy to theorize the establishment of a local reaction, such an infection, followed by dissemination of noxious products which "prepare" the vasculature for subsequent injury. Although this may provide us with a rational explanation for the sequence of events it does not lead us any closer to the basic etiology of allergic vasculitis.

The striking similarity between the nodular dermal allergide of Gougerot and the allergic cutaneous arteriolitis of Ruiter is admitted by both authors and each would be happy to include in his group the cases described by the other. Binkley[1] considers nodular dermal allergide as a less severe form of dermatitis nodularis necrotica. The broadening concept of dermatitis nodularis necrotica and of pyoderma gangrenosum which now includes polymorphic skin eruptions as well as the necrotic nodular lesions fortifies Binkley's conclusion.

In contrast to dermal vasculitis, skin or mucous membrane lesions are not uniformly present in hypersensitivity angiitis and necrotizing angiitis. When they occur the clinician is provided with an accessible site for clinical and morphologic examination of diagnostic value. This is well illustrated in Case 1 which was clinically classical of Wegener's granulomatosis with the diagnosis confirmed by biopsies of the nasal mucosa and skin. However, the postmortem examination revealed non-specific polyarteritis involving the respiratory tract, spleen and kidney.

The second patient seems to have experienced many of the diseases under discussion during her seven years of illness. There was also the history of sensitivity to foods and drugs before the development of nodular dermal allergide. During its prolonged course the polymorphic lesions, particularly the ulcerated nodules, imitated the lesions seen in dermatitis nodularis necrotica or pyoderma gangrenosum. Later shock and subarachnoid hemorrhage followed ingestion of aspirin. Potassium iodide internally caused an exacerbation of symptoms and locally produced a lesion indistinguishable from a spontaneous lesion. During an acute attack there

was pneumonitis suggestive of allergic angiitis. During the long course of the disease atrophic rhinitis, ulcerations of the nasal fossae and tongue, and hypopharyngeal masses of granulomatoid structure developed. From observation of this highly allergic patient and her various clinical patterns it would seem that the diseases outlined in this report may represent varying degrees of allergic vasculitis.

SUMMARY

Cutaneous arteriolitis or nodular dermal allergide, dermatitis nodularis necrotica, pyoderma gangrenosum, hypersensitivity angiitis, allergic granulomatosis with asthma, and Wegener's granulomatosis have been briefly summarized with emphasis on the cutaneous lesions.

A case of classical clinical Wegener's granulomatosis with necropsy is reported.

A case of an allergic patient with chronic dermal vasculitis, respiratory and paranasal lesions is presented.

Study would suggest that the above diseases represent varying degrees of allergic vasculitis.

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THE VALUE OF CLINICAL RESEARCH

So far I have been arguing that every doctor in clinical practice has opportunities for research and that all new discoveries in medicine must begin with the observations of the practitioner. This in turn leads to the conclusion that clinical research is of fundamental value for the pursuit of knowledge. But it has a value of its own for the practitioner. It is not only an absorbing hobby, it represents a state of mind which is healthy, vigorous and alert. A man who is research minded will never become dull and disinterested. His only regret will be that life is too short for all the interest it contains.—SIR CHARLES SYMONDS: The Value of Clinical Research, *Central African J. Med.*, 3:10 (Oct.) 1957.

PULMONARY DENERVATION AND RESECTION IN ASTHMATIC PATIENTS

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THE "tyranny and cruelty" of asthma, its vagaries and its unpredictable response to therapy have been repeatedly referred to in writings during the past three centuries. Few other syndromes have such complexity. Asthma is based etiologically upon allergy, infection, mucosal changes, secretion elimination, disharmony of the autonomic nervous system and psychoneurosis. Structural changes in the bronchial system or lung may precede or develop as a sequel to asthma. The ingenuity of the doctor who cares for these sufferers is taxed to the limit. Although asthma is primarily a medical disease, mechanical problems may occasionally present themselves which call for surgical consideration.

The interest of thoracic surgeons in the problem of the asthmatic patients was a natural and inescapable development.

1. An attack of status asthmaticus may require bronchoscopic aspiration under anesthesia. Occasionally, tracheotomy is indicated. These emergencies bring their plight to the attention of the surgeon.

2. Asthmatic patients with associated diseases may require surgical consideration. Such conditions include: (a) cancer, (b) tuberculosis, (c) cysts or bullous emphysema, (d) pulmonary or mediastinal lymphadenopathy, (e) bronchostenosis, and (f) bronchiectasis.

3. An attack of acute bronchospasm occasionally develops during the course of thoracic exploration. The surgeon then has an opportunity to observe the behavior of pulmonary segments in their response to alterations of intrabronchial pressure. General or localized air trapping is common when bronchospasm occurs. The surgeon may also study directly what is the immediate effect of denervation upon the ingress and egress of air from the moving, breathing lung.

HISTORICAL

As early as 1840, Williams[1] investigated the nerve control of the bronchial musculature. In 1842, Longet[2] demonstrated motor fibers in the vagus. A number of other studies were made in the next fifty years. However, the works of Dixon and Brodie[3] in 1903, on the vagus nerve and Dixon and Ranson[4] in 1912, on the sympathetic nerve were outstanding. They clearly established the role of each autonomic nervous system in the control of bronchial musculature. Since these publications, there has been general acceptance of these facts.

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1. Both systems carry bronchoconstrictor and bronchodilator fibers.
2. Bronchoconstrictor fibers largely run in the vagus.
3. Bronchodilator fibers largely run in the sympathetic.
4. The pulmonary plexus receives sympathetic fibers largely from T1, T2 and T3.
5. Crossing of fibers from both systems is common.

An attempt to interrupt the nerve control of the lung for the bronchospastic disease known as asthma was a logical sequence. In 1923, Kummel[5] advised cervical and stellate ganglion resection. In 1924, Kappis[6] divided the vagus trunk below the recurrent nerve.

In 1929, Phillips and Scott[7] and in 1938, Rienhoff and Gay[8] advised and carried out a division of all visible nerves entering the pulmonary hilum. In 1950, at the meeting of the American Association for Thoracic Surgery, three presentations on denervation for asthma were given. Klassen *et al*[9] reported on results of vagal section and stressed the importance of bilateral denervation. Abbott *et al*[10] combined upper thoracic sympathectomy and plexectomy. Destroyed segments, if present, were removed. Blades *et al*,[11] emphasized the importance of a complete plexectomy. This was accomplished by dividing all vagal branches which enter the pulmonary hilum plus the removal of the adventitia of the vessels. Overholt, Walker and Woods[12] called attention to hidden bronchietasis in the asthmatic patient and reported on combined resection and denervation. Kux[13] described a closed method of nerve cutting and their destruction by cautery. He induces a pneumothorax and then inserts a thoracoscope, cautery and forceps through a cannula. A recent paper appeared in the *Journal of Thoracic Surgery* by Dimitrov *et al*[4] of Budapest. They perform a combined sympathectomy and vagal branch section.

In 1949, Nakayama[15] reported on benefit in more than two out of three severe asthmatic patients treated by the removal of the carotid body—glomectomy. He contends that the influence of the carotid body on respiration is due to sympathetic impulses generating there as a result of alteration in O^2 and CO^2 content of blood. At first, he advised bilateral glomectomy. In a recent communication, Nakayama[16] states that unilateral removal is sufficient. Indications and technique have not been altered since his original publication.

It is apparent from a perusal of the literature that the emphasis of almost all surgeons has been on interventions which interrupt the efferent or afferent nerve pathways to the lung. Rarely were studies other than conventional chest x-rays made to determine possible structural abnormality. The approach was to the sympathetic chain or pulmonary hilum without provision for inspection, palpation and testing of the lung itself. The surgeon who performs cervical sympathectomy and resection of the stellate does not see the thoracic contents. The lung is inaccessible to the

operator using a thoracoscope. Only one author in addition to Overholt *et al* mentioned the advisability of removing functionless segments.

In our mechanical efforts to aid sufferers with intractable asthma, our

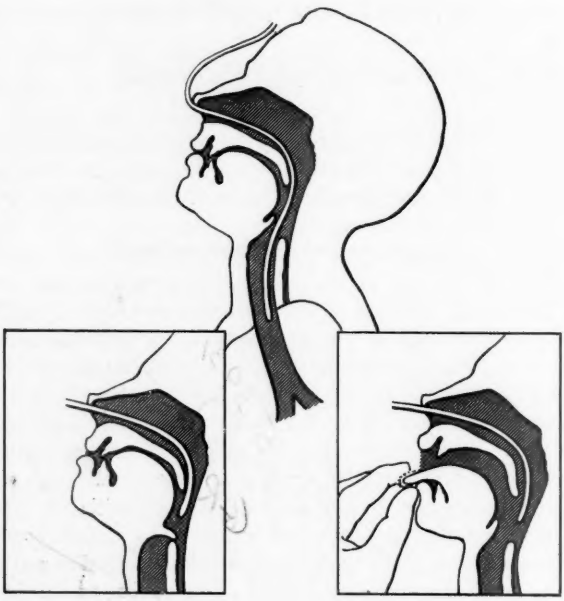

Fig. 1. Sagittal view of upper air passages with catheter in position for injection of contrast media. Left insert shows position of catheter at first stage of insertion. Right insert shows position of epiglottis when tongue is held forward and patient coughs. At this instant, a quick thrust on the catheter will cause it to pass into the trachea.

focus has been on the lung and bronchial system. The primary object of intervention has been to discover if structural abnormalities exist and, if so, to correct them if possible. Denervation is considered a supplementary step to be taken if, after the correction of a structural abnormality, there is evidence of air trapping in healthy segments.*

DELINEATION OF THE BRONCHIAL PATTERN

The greatest amount of information about the bronchial system can be obtained by bronchography. In order to carry out this study in the simplest, quickest and safest way, the following plan is usually followed:

Preparation.—Maximum improvement of bronchospasm is effected by intravenous aminophyllin drip, intermittent positive pressure breathing

*A decade ago, one case of intractable asthma with a normal bronchogram was treated by bilateral upper thoracic sympathectomy without exploring the lung.

with bronchodilating drugs and occasionally detergent aerosols. Specific antibiotic and steroid drugs are employed if indicated. On rare occasions, bronchoscopic aspiration under ether anesthesia is done if an attack of

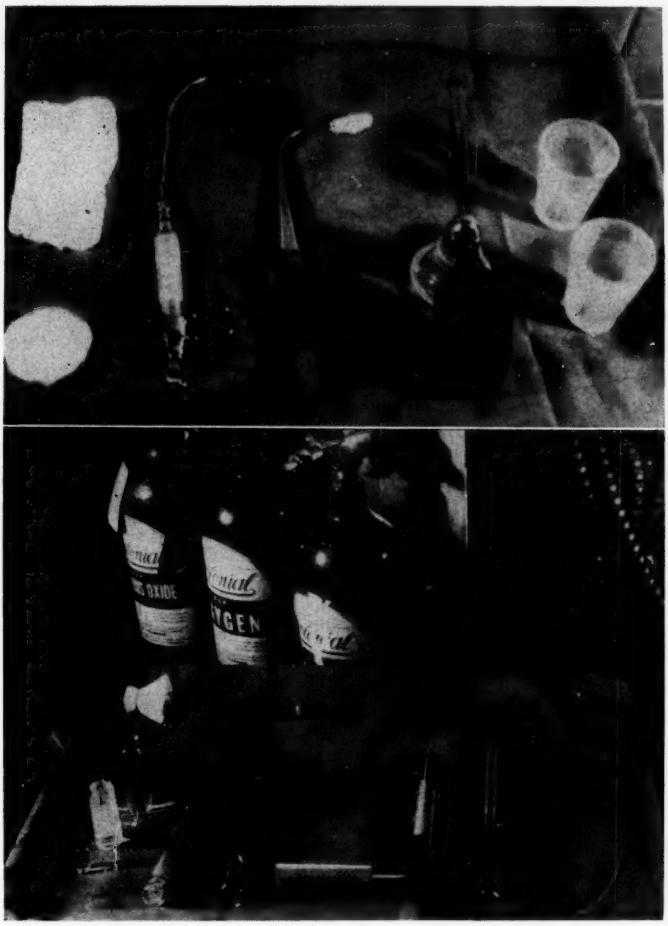

Fig. 2. *(Above)* Simple tray of all materials required for intubation in preparation for bronchography.

Fig. 3. *(Below)* Emergency materials for intravenous medication, intratracheal intubation and equipment for controlled respiration are always kept in readiness when bronchography in asthmatics is performed. An anesthetist accompanies the patient and surgeon to the fluoroscopy room.

status asthmaticus cannot be broken otherwise. In years past, bronchoscopy was always advised in the investigation of asthmatic patients. It was usually carried out immediately prior to bronchography in order to

avoid duplication of topical anesthesia. This practice is now considered unnecessary and unwise except in rare cases. Preliminary instrumentation increases bronchial irritability which, in turn, may result in an incomplete or false bronchogram. Furthermore, inspection of the interior of the bronchial system rarely yields information not pictured by bronchography. If symptoms or signs suggest obstruction, stenosis or tumor of trachea or main-stem bronchus, bronchoscopy is an important step in the preliminary investigation. In asthmatic patients, the issue of surgical intervention hinges more on bronchographic evidence than anything else. Since bronchoscopy is usually advisable at some time prior to exploration, it is expedient in most cases to combine it with intubation for the anesthesia.

Technique.—The following precautionary measures are taken in performing bronchography in asthmatic patients: Emergency equipment is always available. This consists of an antidote for cocaine sensitivity (an intravenous sodium barbiturate), laryngoscope, intratracheal tube, suction, and anesthesia machine and an anesthetist. With proper preparation, untoward reactions are rare. In patients with low pulmonary reserve, the study of each side may be separated by an interval of a few days.

A pre-procedure medication (a barbiturate and atropine) protects against topical anesthetic reactions and vago-vagal reflex action on heart or respiration. The pharynx is sprayed a few times with an anesthetic solution. A catheter is passed via the nose to the posterior pharynx. The patient is asked to cough, and this raises the epiglottis. At that instant, the tube is thrust downward and its tip passes into the upper trachea. The trachea and bronchi are anesthetized by dripping 2 per cent cocaine solution into the catheter. Under fluoroscopic control, contrast media is then instilled. The flow to various segments is controlled by shifting the position of the patient. The pattern is checked fluoroscopically. We prefer to fill the right segments first and take a lateral and right posterior oblique film. The left side is then outlined and three films taken—an antero-posterior and two semi-oblique exposures (left posterior oblique and right posterior oblique at 20°). The catheter is left in place until the films are developed and studied. If any area has been inadequately filled, a repeat injection with specific instillation of the segment in question is done.

BRONCHOGRAPHIC INTERPRETATION

Saccular or tubular dilatation, incomplete stenosis, distortions, crowding or abnormal spread of branches clearly indicate abnormality. Evidence of non-function or mal-function of a segment may be less clear-cut. Often the principal branch will fill, show a normal diameter, but be barren of finer branches. This lack of bronchiolar filling gives a "dead branch" effect in contrast to normal segments which show all the "twigs." In functioning segments, contrast media moves into alveoli and produces the

"foliage" as seen in delayed exposures. The barren or "dead branch" segment never shows alveolarization of contrast media in late films. Complete lack of filling of a segment means one of three things: (1) technical

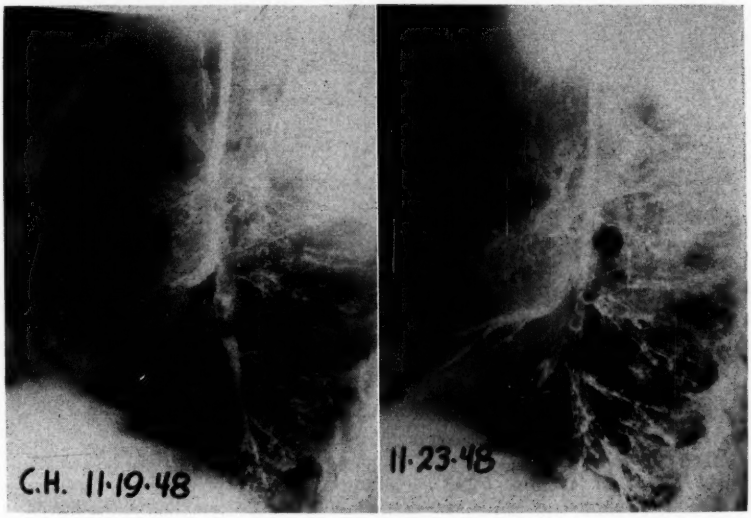

Fig. 4. *(Left)* Mr. C. H. Lateral bronchogram after filling of right bronchial system. Note absence of filling of the middle lobe and incomplete outline of the anterior basal segment.

Fig. 5. *(Right)* Mr. C. H. (Same patient as in Figure 4.) Repeat lateral bronchogram five days after first attempt to outline all bronchi on the right side. The contrast media now outlines the first third of the right middle lobe bronchus. There is no filling of small bronchi or alveoli. Persistence of this defect was adequate evidence of structural abnormality. This fifty-nine-year-old patient had been treated for asthma for eleven months. The bronchial pattern on the left was normal. At right thoractomy, a functionless right middle lobe was removed. The upper and lower lobes "trapped air" and ballooned out to a greater-than-normal volume when under normal atmospheric pressure. After pulmonary denervation and upper thoracic sympathectomy, the lung deflated when intrabronchial pressure was released, and the flow of air in and out of the lung was unimpeded.

error, (2) localized spasm, (3) structural abnormality. Careful preliminary antibronchospastic preparation, unhurried instillation with proper posturing for the segment in question and serial films should eliminate the first two possibilities. Then, serious consideration should be given to the presence of organic obstruction.

INDICATIONS FOR BRONCHOGRAPHY AND EXPLORATION

Patients with mild or controlled asthma or those showing long remissions are obviously not advised to submit to bronchography or be considered for surgical exploration. However, if (1) the asthma was initiated by an attack of pneumonia, (2) subsequent attacks are associated with bronchial infections or (3) the patient has excess bronchial secretion or

difficulty in maintaining clear airways, then bronchography is indicated. Whether or not cases with no demonstrable abnormality be explored depends upon the degree of disability and the burden of the medical regime.

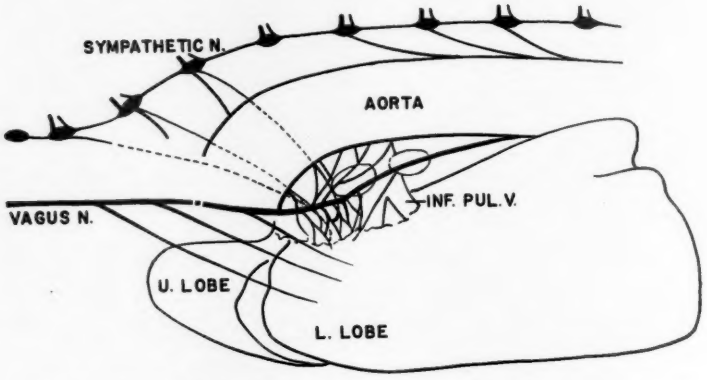

Fig. 6. Drawing of sympathetic and parasympathetic nerve supply of lung as surgeon finds it from postero-lateral approach. Bronchoconstrictor and bronchodilator fibers are found in both systems. The preponderance of the former are found in the vagus and the preponderance of the latter in the sympathetic.

There are three basic reasons for the surgical exposure of the lung in intractable asthma:

1. To remove or correct demonstrable structural abnormality which is in relation to the bronchial system and which may serve as a "trigger mechanism" to perpetuate spasm.

2. To discover, by exploration, structural changes which may not have been revealed by x-ray, bronchography or bronchoscopy.

3. To attempt to relieve abnormal bronchospasm by the interruption of nerve control. Surgical exposure brings the intrathoracic structures into view for direct inspection, palpation, inflation and deflation. This permits actual testing of the segments and visual evidence of the effect of denervation.

CLINICAL MATERIAL AVAILABLE FOR REVIEW

All cases treated in the eleven-year period (1945-1956) have been followed. The health status of patients was ascertained in the first three months of 1958. The period of postoperative observation extends from one to twelve years, the average being four years.

The patients selected for surgical treatment represented a small percentage (15 per cent) of the total number of asthmatic patients seen

(Table I). Likewise, the percentage of patients treated for the combination of asthma and bronchiectasis numbered only thirty-two, this figure being but 4 per cent of the total number of patients in whom the resection was carried out for the latter disease alone (Table II).

TABLE I. INCIDENCE OF SURGERY AMONG 304 ASTHMATIC PATIENTS 1945-1956

Type of Surgery		Patients	Per Cent
No surgery		257	85%
R by surgery		47	15%
Denervation only	15		
Resection only	2		
Resection and denervation	30		
Total		304	100%

The total number of consecutive cases treated in the eleven-year period was forty-seven (Table III). They had been treated under a diagnosis of asthma for six months to thirty-seven years, the average being eleven years.

TABLE II. INCIDENCE OF SURGERY IN ASTHMA AND BRONCHIECTASIS 1945-1956

Type of Surgery	Patients
No surgery	548
R by resection	744
Bronchiectasis and asthma 32 (4%)	
Total (bronchiectasis)	1292

The type of procedure carried out is listed in Table IV. Two-thirds of them required some type of resection of pulmonary tissue. In fact, in eighteen of the thirty-two resection cases, the middle lobe was at fault.

TABLE III. SURGERY R IN ASTHMA 1945-1956

Type of Surgery		Patients	Died Postoperatively	Died Late
No surgery		257		13
R surgery (58 operations)				
Female	31			
Male	16	47	1	5
Total		304	1	18

In more than two-thirds of the cases, a unilateral procedure was done (Table V). An interval of time—several weeks or months—is usually required to assess accurately the degree of improvement following unilateral surgery. Only in the event that benefits were inadequate was a contralateral operation recommended. This principle is also followed in

treating cases of bilateral bronchiectasis. In the majority, a liberation of the burden of disease from the more disturbed side will result in complete relief or sufficient improvement to render contralateral intervention unnecessary.

TABLE IV. SURGICAL PROCEDURES IN ASTHMA

Type of Surgery	Patients	Operations
Resection alone	2	2
Resection and denervation	30	37
Denervation alone	15	19
Sympathectomy	5	
Denervation (hilum)	17	
Denervation and sympathectomy	33	

Four patients who succumbed within the first year have not been used in the appraisal of results.† One patient died in the hospital of a pulmonary embolus on the eighth postoperative day. He had been ill twenty years and was more or less incapacitated during the last nine of them.

TABLE V. UNILATERAL VS. BILATERAL SURGERY

Type of Surgery	Operations
Unilateral	35
Bilateral	11
Denervation 4	
Resection and denervation 7	
Total	46

Three others died within the first year of causes not related directly to the surgery (Table VI). Two of the non-surviving patients lived three and eight years, respectively, then died of heart disease. These have been included since the effect of treatment upon their asthmatic state was determined.

TABLE VI. LATE DEATHS

Patient	Age	Duration Asthma Years	Procedure	Interval	Cause of Death
P.D.	35	6	Bilat.—D.&S.	1 mo.	Aspiration pneumonia
T.S.	44	16	Bilat.—D.&S.	3½ mo.	?
T.R.	54	1½	Bilat.—D.&S. and lingulectomy	7½ mo.	Coronary occlusion
C.M.	58	9	Rt. D.	3 yrs.	Cardiac decompensation
R.C.	59	37	Lt. D. and lt. U. lobectomy	8 yrs.	Cor pulmonale

RESULTS

In appraising benefits, patients were re-examined and the statements of both patients and their physicians were solicited. The summary of

†During the eleven-year period under discussion, there were thirteen deaths among the group of 257 non-surgical asthmatic patients seen by us in consultation. This rate of attrition indicates, in a way, the serious plight of the asthmatic patients who, by selection, are channeled to a thoracic surgical clinic.

these tabulations in forty-three long-term survivors is shown in Table VII. Improvement had to be undisputed or they were classified as the same. In the tabulation of the degree of benefit, it seemed expedient to group them, as follows:

TABLE VII. SURGERY B IN ASTHMA
Follow-up one to twelve years in forty-three long-term survivors

Condition	Patients
Worse	0
Same	2
Better—medication reduced	9
Better—medication occasionally	16
Better—no medication—well	16
Total	43

1. Improved patients who required medication, but in reduced amounts. The majority of patients in this group required some medical supervision.
2. Considerably improved patients who, on occasions, may medicate themselves. They rarely called upon a physician.
3. Those patients in whom asthmatic seizures have been eliminated. These patients enthusiastically reported that they were well.

TABLE VIII.
BENEFITS IN FORTY-THREE PATIENTS

	Resection and Denervation	Denervation Only
Worse	0	0
Same	0	2
Better—reduced medication	6	3
Better—occasional medication	10	6
Better—no medication—well	15	1

Patients in whom "trigger mechanisms" were discovered and removed received the greatest benefits. All were improved to some degree and more than half had been completely relieved of asthma. In Table VIII, the results in those treated by resection plus denervation and those in whom only denervation was performed are compared.

Half of the patients in the denervation-only group were treated more than eight years ago. These early cases were not explored for possible structural abnormality. It was not our practice then to expose the complete hemithorax at the time of denervation, relying on endoscopy and bronchography to rule out the presence of structural defects. Now all of these would have received diagnostic exploration and, in some, pulmonary disease would have been found. These cases, then, would have appeared in the combined resection and denervation group.

The denervation group alone is small, but significant (Table IX). Most patients were sufficiently improved by a single operation so that bilateral

treatment was not recommended. However, the two unimproved cases received only unilateral denervation. In one of these, a contralateral operation was advised. Patients in whom a single lung has been denervated serve as controls. Frequently, they report, and examination substantiates, the persistence of only a contralateral wheeze.

TABLE IX. BENEFITS IN TWELVE PATIENTS — DENERVATION ONLY

	Unilateral	Bilateral
Worse	0	0
Same	2	0
Better—reduced medication	2	1
Better—occasional medication	5	1
Better—no medication—well	1	0

SUMMARY

1. Intractable asthma may be perpetuated by structural abnormalities in bronchopulmonary segments which act as "trigger mechanisms."

2. Bronchography, if carefully done, is safe and often productive of useful circumstantial information necessary for successful management.

3. Surgical exploration permits direct inspection of the lung and testing of segments as to inflow and egress of air. Mechanical defects can be corrected forthwith and sympathetic, parasympathetic or both denervations carried out simultaneously.

4. Long-term studies of this direct approach in intractable asthma have shown varying degrees of betterment with substantial improvement in the health status of two-thirds of the patients.

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DEFINITION AND DESCRIPTION

A hypothesis is a proposition which seems to explain observed facts and whose truth is assumed tentatively for purposes of investigation. It is a leading question put to nature, a guess designed to suggest the sort of inquiry by which an answer might be reached. The success of the method of hypothesis depends upon the delicate balance between conjectural and empirical elements. We have to construct guesses as to how things are before we can make the observations necessary to determine whether our guesses were correct. The hypothesis, then, is a proposition suspected of being true but lacking the requisite support of evidence, a suggestion that new and necessary relations may exist and should be investigated. A good hypothesis is one that offers a possible explanation or that ascribes an adequate cause.

In other words, a hypothesis is a preconception of what investigation will disclose. It must be a matter about which there is both doubt and some inclination toward belief. Where there is no doubt concerning the truth of the idea, there is no willingness to submit it to the test of experiment. No one would try a proposition already convicted on conclusive evidence, and no one would test a proposition whose truth is not doubted. Without the inclination to belief, there would be no disposition to look into the degree of truth of the hypothesis. For if the hypothesis should be confirmed, it could be used as an instrument in further inquiry. And without the large element of doubt, the propostion would be a simple matter of belief, not a scientific hypothesis.—JAMES K. FEIBLEMAN: The Role of Hypotheses in the Scientific Method. *Perspectives in Biology and Medicine,* Spring, 1959.

AN EVALUATION OF TRIAMINIC® AND HYDROCORTISONE IN THE TREATMENT OF NASAL ALLERGY, NASAL POLYPOSIS, AND ASTHMA

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ALLERGIC DISORDERS, particularly of the respiratory tract, are nearly always characterized by mucous membrane and local tissue edema from vasodilitation, by excessive mucous production, and by smooth muscle spasm. To inhibit or reverse these changes, in which histamine appears to play an important part, a combination of antihistamine and sympathetic-mimetic vasoconstrictor should be useful. Where allergic irritation is particularly pronounced, or when secondary changes have taken place, the addition of hydrocortisone to the treatment should theoretically improve the results. Treatment of symptoms is not a substitute for an attack on the basic cause of the allergic disorder in question, but it is often desirable to give temporary relief while the allergy is being brought under control.

Clinical observations on the oral use of Triaminic (Smith-Dorsey), which contains two antihistamines and a vasoconstrictor amine have been reported by Lhotka[3] and Farmer.[4] Because these two reports deal mainly with the use of Triaminic as a decongestant in upper respiratory infections, the results are not strictly applicable to allergic disease. Hence the study reported here involved patients suffering primarily from respiratory allergy and its complications. Triaminic without and with various amounts of hydrocortisone was evaluated in cases of chronic allergic and vasomotor rhinitis, nasal polyposis, chronic asthma and emphysema.

MEDICATION

Triaminic plain and combined with three different amounts of hydocortisone, plain hydrocortisone in two strengths, and a placebo were prepared, all identical in appearance. The several tablets were identified by code numbers throughout the study, so that their identity was unknown to the patients and the physicians. The formulas of the Triaminic containing tablets are given in Table I.

Half of the ingredients of Triaminic are contained in the outer portion of the tablet, which dissolves at once, and the remainder in a core that disintegrates three or four hours after ingestion. In this way the action of the medication is prolonged from six to eight hours. When added to the Triaminic, hydrocortisone was in the outer portion of the tablet in each case. The hydrocortisone tablets contained either 5 mg or 10 mg.

Triaminic is a trademark of the Smith-Dorsey Division of The Wander Company, through whose generous support this study was made possible.

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TABLE I. TRIAMINIC FORMULAE

	Triaminic	Triaminic "2.5"	Triaminic "5"	Triaminic-HC
Pheniramine maleate	25 mg	25 mg	25 mg	25 mg
Pyrilamine maleate	25 mg	25 mg	25 mg	25 mg
Phenylpropanolamine hydrochloride	50 mg	50 mg	50 mg	50 mg
Hydrocortisone	—	2.5 mg	5 mg	10 mg

The use of antihistamine mixtures has been shown by Sure, Sievers and Harris,[13] by Steinberg,[12] and by Wittich,[15] among others, to be preferable to single compounds, in that the therapeutic effect of the individual compounds is retained, but the overall side effects are reduced. Prophenpyridamine maleate and pyrilamine maleate form such an antihistamine mixture.

The vasoconstrictor of Triaminic is phenylpropanolamine, an effective sympatheticomimetic amine which produces vasoconstriction in the nose after oral administration, but which causes relatively little central stimulation.[3]

PART I. CHRONIC ALLERGIC RHINITIS

Chronic allergic rhinitis is a common complaint in Southern California, where plant pollens are produced ten months of the year, and where climatic factors favor the presence of allergic irritants in the air except during the short rain season. The condition is marked by nasal obstruction from swollen edematous turbinates, rhinorrhea and post-nasal drip, attacks of sneezing (often early in the morning) and the consequences of impaired nasal breathing. The mucous membranes of the nose are usually pale and thickened, polyps may be present, and the nasal mucous may contain eosinophiles. Skin sensitizing antibodies are nearly always present. Although there may be seasonal exacerbations, symptoms tend to be present all year.

Thirty patients with fairly uniform symptoms of chronic allergic rhinitis co-operated in this part of the study. They ranged from fourteen to sixty-six years of age. The median age was thirty-six and a half years. Symptoms had been present for at least two years in all cases. All gave positive reactions by skin test to inhalant allergens, but had not responded well to routine desensitization. Patients in whom there were signs of nasal infection were excluded from the study.

Each patient kept a daily record on standard forms of symptoms referable to the eye, ear, nose and throat. Medication other than the trial tablets, such as nose drops or antihistaminic agents was recorded at the same time. Every effort was made to have the patient keep his record up to date, and the chart was carefully reviewed at each weekly visit. Patients new to the clinic were usually asked to keep records for a preliminary period until they became familiar with the method. The number of symptoms and the amount of medication for each week was recorded as the Symptom Index and Medication Index respectively.

Each patient was also asked to provide a weekly estimate of subjective improvement, if any. This was graded from None to Complete Relief on a scale of zero to four. This estimate was checked by examining the nose each week under standard conditions, noting the amount of obstruction present and the condition of the mucous membrane. Side reactions were asked for in as nondirectional a fashion as possible.

Triaminic by itself was not used in this part of the study, since the purpose was to determine whether the addition of Triaminic to small doses of hydrocortisone improved the treatment of chronic rhinitis. The patients in this group were placed for two weeks each on Triaminic "5," Triaminic "2.5," hydrocortisone 5 mg, and the placebo. The dose was one tablet three times a day for all preparations.

By following a random order of rotation from one preparation to the next, approximately equal fractions of the group were on each of the four preparations at any given time. This tends to minimize the effect of external factors on the group as a whole.

TABLE II. AVERAGE RESPONSE TO MEDICATION FOR TWO WEEKS BY THIRTY PATIENTS WITH CHRONIC ALLERGIC RHINITIS

Medication(a)	Symptom Index(b)	Medication Index(c)	Degree of Relief(d)
Triaminic 5	18.6	10.0	2.6
Triaminic 2.5	18.1	11.0	2.3
Hydrocortisone 5 mg	23.8	12.8	1.2
Placebo	27.0	13.4	0.7

(a) One tablet t.i.d.
(b) Average number symptoms/wk.
(c) Average amounts medication/wk.
(d) Range: 0=no relief to 4=complete relief.

RESULTS

Table II summarizes the results obtained in the thirty cases of chronic rhinitis.

All three indices showed that the two Triaminic preparations are almost identical in effect. The various indices for hydrocortisone alone were about midway between the placebo and the Triaminic compounds. In respect to the "Degree of Relief" noted by the patients and confirmed by nasal examination, the Triaminic preparations were about twice as effective as hydrocortisone and three times as effective as the placebo.

Since doubling the hydrocortisone combined with Triaminic had no significant effect on the results, it appears that this amount of the steroid is too small to influence chronic allergic rhinitis. The relief experienced in this group may be attributed mainly to the Triaminic.

It may be noted that there was not much difference between the values for the Medication Index from one preparation to the next. This probably reflects the habit among patients with chronic nasal allergy of taking medication without much regard to actual symptoms.

PART II. CHRONIC ASTHMA

To be effective when used as the only medication in chronic asthma, hydrocortisone in amounts exceeding 40 to 60 mg per day is usually needed.[1,2,9] It was one of the purposes of this study to discover whether smaller doses, in the range of 15 to 30 mg added to Triaminic might not result in relief of symptoms without producing the undesirable signs of hyperadrenalism.

Twenty-one asthmatic patients from the Los Angeles County General Hospital Allergy Clinic co-operated in this part of the study. They ranged in age from twenty-eight to seventy-nine years, the median age being forty-nine years. All suffered from chronic asthma of two or more years duration, and many were life-long asthmatics. The median for duration of symptoms was eleven years.

Severity of asthma was judged moderate in twelve cases, that is, the asthma prevented working, and it was necessary for these patients to use oral medication or epinephrine by inhalation several times a day. Nine patients had severe asthma, that is, in addition to the use of home medication they had a record of frequent admissions to the hospital for emergency treatment.

Triaminic "5," hydrocortisone 5 mg and the placebo were used three times daily in succession by these patients for three weeks on each preparation. Also in this group, approximately equal numbers were taking each type of medication at a given time, to minimize climatic and other factors that might influence asthmatic symptoms.

Each patient kept a daily record of symptoms and of all medication used in addition to the tablets being tested. Again every effort was made to get as accurate a record as possible, and patients who had been unreliable in the past were not included in this study. The Symptom Index was derived from the weekly records by averaging the attacks per week, and the Medication Index calculated from the amount of extra medication taken each week.

As a cross-check, each patient was asked to give an estimate of the degree of relief obtained, as compared to his usual state. As in the case of the patients with chronic rhinitis, this was graded from zero to four, and the average Degree of Relief for the three-week period was used in tabulation.

Once a week during the control period and throughout the study, each patient was checked for Timed Vital Capacity (T.V.C.) and Maximal Breathing Capacity (M.B.C.) using a 13.5 liter Collins Recording Spirometer. Readings were taken with the patient standing, at mid-morning, after a rest of at least one half hour. Only the first three seconds of the vital capacity curve were used. Maximal breathing was recorded for fifteen seconds, and calculated as liters per minute.

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TABLE III. AVERAGE VALUES OF SYMPTOMS, MEDICATION, T.V.C., AND M.B.C. IN TWENTY-ONE ASTHMATIC PATIENTS DURING THREE WEEKS OF TREATMENT

Medication	Average Weekly Symptom Index		Average Weekly Medication Index		Average Weekly Relief Index		T.V.C. 3-Week Average		M.B.C. 3-Week Average	
	3 Weeks*	2 Weeks**	3 Weeks *	2 Weeks**	3 Weeks*	2 Weeks*	Value	Per Cent of Normal	Value	Per Cent of Normal
Triaminic "5" t.i.d.	34.8	33.2	30.9	30.9	1.50	1.57	1.94L	58.8	34.4 L/min.	43.0
Hydrocortisone 5 mg t.i.d.	33.6	32.0	28.3	26.9	1.49	1.43	1.95L	59.8	34.0 L/min.	42.5
Placebo t.i.d.	40.5	41.0	34.4	33.2	0.73	0.67	1.84L	56.5	30.9 L/min.	38.6

*Average per week for three weeks.
**Average per week for second and third week only.

RESULTS

Table III summarizes the results in the twenty-one cases of asthma. Because the first week on any one of the medications might have been influenced by "carry-over" from the previous treatment, the various indices have been calculated for second and third weeks only, as well as for all three weeks of each trial period. Since no carry-over effect was found, the lung function data have been presented only for the entire three weeks in each case.

Values for T.V.C. and M.B.C. are given both in the average of actual measurements, and as per cent of "Expected Normal." This latter figure was calculated from the following formulae of Motley[10] and West.[15]

Vital Capacity	Males	$2.5 \times M^2$ body surface area
	Females	$2.0 \times M^2$ body surface area
Maximal Breathing Capacity	Males	$96 - \text{Age}/2 \times M^2$ body surface area
	Females	$83 - \text{Age}/2 \times M^2$ body surface area

There was little difference between Triaminic "5," 5 mg of hydrocortisone, or the placebo as far as the weekly total of asthma attacks or the use of symptomatic medication was concerned. The figure for the degree of subjective relief, however, was twice as good for the two active preparations as for the placebo. This suggests that hydrocortisone, the common factor in the two preparations, even in doses of 15 mg a day, produces an increase in the sense of well being, without affecting lung function to any significant extent.

The figures for the average Three-Second Vital Capacity and the Maximum Breathing Capacity were essentially the same for the active preparations and the placebo. When converted to per cent of expected normal, the average for these functions is low. T.V.C. was less than 60 per cent of normal, and M.B.C. was between 30 per cent and 35 per cent. These figures confirm the clinical observations concerning the severity of asthma in this group.

PART III. NASAL POLYPOSIS.

During the first part of the study it was noted that small nasal mucous polyps present in some of the cases of chronic rhinitis decreased in size or disappeared during the time Triaminic with hydrocortisone was being taken. Because these mucous polyps can present a serious problem in treatment and prevention, a group of patients whose major complaint was nasal polyposis or polypoid degeneration of the turbinates was selected for trial on Triaminic and hydrocortisone.

When looked for carefully, nasal mucous polyps may be found in as many as 5 per cent of cases of chronic rhinitis, and in 30 per cent of cases of chronic asthma.[6] Since the pioneer work of Kern and Schenck,[6,7] it has been generally accepted that nasal mucous polyps are allergic in origin. An important cause of their formation appears to be the constant

vasodilation and mucous membrane edema that accompanies the allergic insult. Arising from the lateral walls and roof of the nose, and from sinuses, these growths may cause complete nasal obstruction, resulting in imparied sinus drainage, chronic infection, anosmia, and the sequelae of mouth breahting.[11]

TABLE IV. EFFECT OF ORAL TREATMENT WITH TRIAMINIC AND HYDROCORTISONE ON TWENTY-SEVEN CASES OF NASAL POLYPOSIS

Medication	Improved	Not Improved
Triaminic + 10 mg hydrocortisone	24 (89%)	3 (11%)
Triaminic	17 (63%)	10 (37%)
Hydrocortisone 10 mg (24 cases only)	13 (54%)	11 (46%)
	Retained Improvement	Relapsed
Triaminic following Triaminic+10 mg hydrocortisone (20 cases)	13 (65%)	7 (35%)

It is well known how rapidly mucous polyps can regenerate after surgical removal, and many a patient has undergone repeated polypectomies without permanent relief. Control of the allergic factor usually will retard, but may not entirely prevent recurrence after removal. And as pointed out by Jones,[5] anti-allergic treatment alone does not cause regression of well established polyps. Therefore, a reliable medical adjunct to allergic treatment is highly desirable.

The preparations used in this part of the study were Triaminic, Triaminic-HC (10 mg hydrocortisone per tablet) and hydrocortisone 10 mg. Hydrocortisone in doses adequate to control asthma was reported by Arbesman and Richards[1] to cause shrinkage of nasal polyps in five of six cases. The dose used, ranging from 40 mg to 80 mg a day, caused over 20 per cent of their patients to show signs of hyperadrenalism. MacLaren and Frank[9] found that hydrocortisone in doses below 40 mg a day could be tolerated for long periods by the majority of their patients. It was decided therefore, to limit the hydrocortisone used by the patient with nasal polyposis to 30 mg or less a day.

Twenty-seven patients with various degrees of nasal polyposis associated with chronic vasomotor (allergic) rhinitis were given each type of medication for two weeks in random order. The dose in each case was three tablets a day during the main trial period. Subsequently lower doses of Triaminic and Triaminic-HC were used to establish maintenance levels.

In the group of twenty-seven patients there were nine males and eighteen females. The age range was seven to seventy years, with the median at forty-three years. Bilateral mucous polyps were present in twenty-one; unilateral in one. There remained seven cases of marked polypoid degeneration of the turbinates. Polypectomies had been performed on fourteen, or about half of the patients. Three had been operated on once, four twice,

two thrice, and one each for four, five, six, seven and eight times. Positive skin tests to common environmental allergens such as house dust, animal dander, mold spores, etc., and to pollens were found in twenty-two of the twenty-seven patients, an incidence of 81.5 per cent.

Before treatment was started, and once a week throughout the study,

TABLE V. PATIENTS WITH NASAL POLYPOSIS BEFORE AND AFTER TREATMENT WITH TRIAMINIC-HYDROCORTISONE: NUMBER OF CASES IN EACH RANGE OF OBSTRUCTION

Amount of Nasal Obstruction	0-24%	25-49%	50-74%	75-100%
Before treatment	0	2	10	15
After Triaminic-HC	10	11	6	0

the extent of obstruction in the nose produced by the growths on each side was estimated, and the average for both nostrils recorded. Note was also made at each weekly visit of any comments the patients made in regard to nasal breathing, drainage, pain, sense of smell, and any side effects from the medication.

RESULTS

The data presented in Table IV shows that during the two weeks the patients took Triaminic-HC, twenty-four (89 per cent) showed improved nasal airway due to shrinkage of polyps, and three (11 per cent) were either no better or may have been worse. During the time the patients were on Triaminic only, seventeen (63 per cent) were improved, ten (37 per cent) were not. Due to technical difficulties, not all patients were able to complete the two weeks on hydrocortisone alone. Of the twenty-four that did, thirteen (54 per cent) improved and eleven (46 per cent) did not.

On the basis of this series of patients, it appears that Triaminic and hydrocortisone together had a decided effect in decreasing the extent of nasal polyposis, and the combination is more effective than either one alone.

Also shown in Table IV are the twenty cases who used Triaminic after Triaminic-HC. Improvement was either maintained or increased in thirteen (65 per cent) but relapse was found to occur in seven (35 per cent). In other words, two-thirds of the cases could be switched to Triaminic after the polyps had been reduced by combined use with hydrocortisone, but one-third could not.

After the main portion of the study was completed, fourteen patients were allowed to continue for two to four weeks on Triaminic-HC at the reduced dose of two tablets a day. A gradual return of polyposis was found in four (29 per cent) but ten (71 per cent) were able to maintain their improvement

The rate and extent of response to Triaminic-HC was occasionally dramatic. A large mucous polyp could be seen to start wrinkling in forty-eight hours, and in two weeks a growth that had been causing complete nasal obstruction would be reduced to one-third or less of its original size.

When the twenty-seven cases are divided into four groups depending on the extent of nasal obstruction present, and compared before and after treatment with Triaminic-HC, the data shown in Table V is obtained. Before treatment, for example, there were no patients with less than 25 per cent obstruction, and fifteen patients with more than 75 per cent obstruction. After Triaminic-HC, there were no patients left in the group experiencing 75 per cent or more obstruction, but ten had moved to the "less than 25 per cent" category. The intermediate categories of obstruction showed a similar reversal in numbers. In two cases, growths disappeared entirely.

SIDE EFFECTS

Side effects from the various preparations were not marked except in three cases. Three patients with rhinitis discontinued the use of Triaminic shortly after the beginning of the study because of nervousness, insomnia or gastric distress.

Somnolence ranging from slight to moderate was noted by 18 per cent of the patients on Triaminic and hydrocortisone combinations. Twenty per cent noted some nervousness, and 8 per cent, mild insomnia. Complaints each mentioned once or twice were headache, slight vertigo, muscular pains and gastric burning.

No evidence was found of hyperadrenalism, such as edema, rapid weight gain, hirsutism, acne, elevated blood pressure, or gastric ulcer, in the patients taking hydrocortisone.

Two patients noted somnolence and one noted nervousness from the placebo.

DISCUSSION

In chronic allergic rhinitis there appeared to be no difference in effect between Triaminic with 2.5 mg and 5 mg of hydrocortisone added to each tablet. The total dose of steroid in either case was too small to influence the result. An equivalent amount of hydrocortisone alone was less effective, suggesting that such benefit as observed came from the Triaminic.

The chronic asthmatics all had extensive reduction of lung function, so that it was not unexpected to find that small doses of hydrocortisone (up to 30 mg a day) added to Triaminic had almost no more effect than a placebo on objective symptoms and lung measurements. Had these been mild cases of asthma the combination of antihistamines and phenylpropanolamine might have had a detectable effect.

The same type of result was found in a group of ten patients with emphysema that are not included in this report. They used first Triaminic-

HC and then Triaminic four times a day for four weeks. Only one showed a significant increase in lung function measurements, although half the group thought they felt better on Triaminic-HC.

The increased sense of well-being usually noted by the patients with pulmonary disease, even on low doses of hydrocortisone, is a common finding. Only in the cases of nasal polyposis, where 10 mg of hydrocortisone was used in each Triaminic tablet did the combination with steroid appear to have a definite advantage over the separate portions. This effect might have been observed in the series on chronic allergic rhinitis had the same amount of hydrocortisone (30 mg a day) been used, but it was not thought desirable to use steroids in a condition that could be controlled without them.

The long-term benefits from the use of Triaminic-Hydrocortisone type of treatment in nasal polyposis have yet to be evaluated. Twenty patients from the original group are still using, after seven to ten months, various schedules of Triaminic and Triaminic-HC, and are keeping their symptoms under control. Temporary relapses are likely to follow sinus or upper respiratory infections, which will usually respond to antibiotics. As is common in chronic allergic disease, "escape" from the restraining effect of medication may appear spontaneously and last for a variable length of time. In some cases where Triaminic-HC was discontinued and polyps enlarged again, resumption of treatment was not as effective as the first time. The reason for this is not clear, but similar behavior is often noted in the use of adrenal steroids for allergic disease.

Because of the high rate of return of mucous polyps when medication was discontinued or reduced too far, it is clear that this treatment alone is not enough. For long term control, allergic desensitization and avoidance when possible of specific antigens must be included. For rapid relief, however, of severe nasal obstruction due to polyps while other measures are being brought into us, Triaminic-HC appears to be a very useful medication. Only further experience will show what may be the optimal combination of treatments.

SUMMARY

1. Triaminic is an extended action tablet containing pheniramine maleate 25 mg, pyrilamine maleate 25 mg, and phenylpropanolamine hydrochloride 50 mg.

2. In thirty patients with chronic allergic rhinitis, three tablets daily of Triaminic with 2.5 mg or 5 mg of hydrocortisone were equally effective, and produced more relief than a placebo or an equivalent amount of hydrocortisone alone.

3. In twenty-one chronic asthmatic patients with moderate to severe disease, three tablets a day of Triaminic with 5 mg of hydrocortisone and hydrocortisone 5 mg alone were no more effective than a placebo in improving lung function or decreasing symptomatic medication.

4. Triaminic with 10 mg of hydrocortisone taken three times a day was more effective in cases of nasal polyposis than Triaminic or hydrocortisone separately. Twenty-four of twenty-seven cases, or 89 per cent, were improved on the combination, as compared with seventeen or 63 per cent on Triaminic. Thirteen of twenty-four cases, or 54 per cent, were improved on hydrocortisone alone. Relapses were frequent when the medication was discontinued, but 65 per cent of the patients could maintain improvement on Triaminic for long periods of time.

5. Triaminic with added hydrocortisone is not effective in moderate to severe asthma, but appears to be a valuable medication for the temporary control of nasal mucous polyps.

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ASPIRATION FOR TRUTH

And when we ask ourselves who among the philosophers has done most to foster that aspiration, our thoughts immediately go out to Plato. And we call to mind in particular that passage in the Phaedo which says that all who have any sort of strength of mind should be prepared to sail out dangerously as on a raft upon whatever idealistic human argument may give bravest promise of holding its own against destructive criticism.—SIR ALMROTH WRIGHT: Prolegomena to the Logic which Searches for Truth, London, William Heinemann Ltd.

THE TREATMENT OF NASAL POLYPOSIS

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THE proper method of the treatment of nasal polyps is one of the most controversial in the field of otolaryngology. The great number of contributions to the literature on this subject, the varied methods of treatment described, the various theories as to the cause of polyps and the wide variations in results of treatment, certainly attest to the validity of this thesis.

It is the belief of the writer that at the present time there is no one means by which nasal polyps can be successfully cured; and it is a question, if, in the light of present-day knowledge, we do have a cure. It is true that in many cases polyps have been surgically removed and have shown no recurrence, but possibly, some variable time later the patient has had further surgery.

This writer is of the belief that the best means of treating polyps is by using a combination of methods known to be effective in the control of polyps. In some instances, simple surgical removal is effective—in others, radical surgery of the sinus to the point of pansinusectomy is required. Polyps have been seen to disappear by using the proper diagnostic and therapeutic methods at our disposal for treating allergic disorders. More recently, steroid therapy has come into use by topical treatment in the nose or by oral dosage. Steroid sprays, in conjunction with antihistaminic and steroid agents injected directly into polypoid tissue, have given good results.

When a patient presents large obstructing or protruding polyps, the obstruction should be removed as soon as possible for the relief of his immediate distress. This can often be done in the office by means of removing one or two large obstructing masses, thus giving him an adequate breathing space.

The extent of surgical intervention is at the discretion of the operator. Some prefer intranasal polypectomy; others prefer more radical removal with exenteration of all the sinuses.

Recently, Simonton[5] in an excellent discussion on surgical removal of polyps concluded that: "A comprehensive operation to remove all polyps and potential polyp-bearing mucosa from the nose and sinuses produces better results than more conservative surgical measures." It seems that this conclusion is rather drastic, inasmuch as to remove all potential polyp-bearing tissue would require the removal of all the intrasinal and intranasal mucosa.

Presented at the Fourteenth Annual Congress of The American College of Allergists, Atlantic City, New Jersey, April 25, 1958.

Grossly, polyps are classified in groups of I to IV, depending on their size and degree of obstruction:

Group I. Small meatal polyp with no pedunculation.

Group II. Somewhat larger polyps than seen in Group I with pedunculation.

Group III. Large meatal polyps obstructing the meatus and the sinus ostia, partially obstructing the breathing space.

Group IV. Large polyps obstructing breathing completely, often protruding from the nares, sometimes can be seen without the aid of a nasal speculum.

Generally, the polyps appear pearly grey and glistening, with marked edema. Some polyps, however, exhibit an inflammatory reaction, usually due to secondary infection and vascular infiltration; others may exhibit crusting or surface ulceration.

The histopathologic changes which occur in nasal allergy and polypoid degenerations have been thoroughly described by Hansel[2] and more recently by Semenov.[4] These changes take place in the three constituents of the membrane: the epithelium, basement membrane and the tunica propria or subepithelial layer. The epithelial layer often is entirely absent or may show hyperplasia. At times both may occur in the same specimen; usually there is a loss of the ciliated cells and on some occasions there is an alteration to squamous epithelium and also a marked increase in the number of goblet cells. The basement membrane is usually thickened in polyps due to allergy, but on other occasions, it may be edematous with some widening between the cellular elements, or entirely absent. The most marked changes occur in the tunica propria or the subepithelial layer which are characterized by edema and cellular infiltration of eosinophils and fibroblasts. It is in this area that we find the capillary bed, fibrous connective tissue, and glandular structures.

Edema is caused by increased capillary permeability. This takes place first in the area just below the basement membrane where the capillaries are most abundant. In marked edema of long standing, the tendency toward polyp formation is the greatest. The connective tissue becomes so water-logged and filled with fluid that there is a widening of the intercellular spaces resulting in polyp formation. The cellular infiltration is most marked just below the level of the basement membrane. Here the eosinophils are most numerous and abundant; however, lymphocytes and plasma cells are also noted in this area.

It is believed by the writer that polypoid changes in the nasal and sinal mucous membranes, in the majority of instances, are of allergic origin, and that the failure to apply the proper anti-allergic management in these cases is often responsible for the recurrence of these growths. On the other hand, they seem to recur sometimes no matter what approach is

used. This only means that continued investigation and improved methods of therapy will remain necessary before the true solution is reached.

In order to institute proper management of the allergic patient, it is necessary to obtain a complete clinical history followed by an adequate physical examination and the essential laboratory procedures.

Anderson and Rubin[1] have recommended an extensive and detailed questionnaire, which, if used, will give one a great deal of information as to the background of the patient. Any special data can be added as is necessary.

Cytologic study of the nasal secretions as recommended by Hansel[2] should be made; using the Hansel stain, he determines the relative degree of eosinophils or neutrophils present, and thus is able to correlate allergy with infection.

Hansel has demonstrated that in the presence of allergy, the number of eosinophils may be 4-plus in a stained slide, but, if infection is superimposed, the neutrophilia may be greatly increased, thus reducing the number of eosinophils present. Further, as the infection is reduced or cleared, there will be a return to the previous degree of eosinophilia.

X-ray studies of the paranasal sinuses are essential; they can offer the clinician valuable information in the differential diagnosis between allergy and infection. If the x-rays reveal a marked clouding of a single sinus or group of sinuses, one should consider this an indication of an infectious sinusitis. On the other hand, if there is present a mild clouding of all the paranasal sinuses, one should consider the possibility of an allergic condition. Masses seen in the sinuses, particularly the antra, should receive additional attention with the differential diagnosis being either mucocele, polyps or true neoplasms.

Skin testing in allergic patients can be basic, using a minimal number of allergens, or complete.

Desensitization therapy should be instituted as soon as possible in an effort to bring the allergic fraction of the problem under control.

The low optimum dosage or maintenance dosage therapy as recommended by Hansel[2] is preferred to the more concentrated or buildup dosage used by others. When using low dosage therapy, the chance of local and constitutional reaction is negligible. The dilutions vary between 1:1,000,000 and 1:1,000,000,000. Once the proper dilution and dosage have been reached, the dosage should remain at that level, the only necessary change being a lengthening of interval between injections.

Antihistaminic drugs, as well as the sympathomimetic drugs, such as ephedrine and epinephrine, are quite useful in the control of allergic symptoms, but then only as long as they are administered under a continuous dosage regime.

The writer[3] recently reviewed much of the literature regarding the use of the steroid agents in the treatment of allergic rhinitis and nasal polyposis. He presented a method of injecting hydrocortisone-free alcohol

into the substance of the polyps. There were pre-treatment and post-treatment biopsies taken and the results described. He concluded that by this treatment there was a reduction in the edema and cellular elements of the polyps, and that there was no reduction in the fibrous, glandular or cystic changes noted in the pre-treatment biopsies.

During the past year those cases which have been chosen for injection therapy have been treated with Hydeltra T.B.A.®

Pre-treatment biopsies revealed a typical nasal polyp with edema, eosinophils, lymphocytes and plasma cells present in varying degrees. In polyps of the higher grades, there were increasing quantities of fibrous tissue, cystic changes and glandular elements.

The treatment consisted of injection with .05-.10 cc of Hydeltra T.B.A.® into the polyp or polyps on three occasions at weekly intervals. There was a marked reduction in the size of all the polyps. This reduction is attributable to the lessening of the intercellular and intracellular edema of the tissues. It must be borne in mind at all times that we do not expect any effect on the irreversible changes in the tissues previously described. In those cases in which polypectomies have been performed, and there begins a recurrence, this method of treatment has been effective in retarding the regrowth of the tissue, and the patients remained comfortable without further removal for variable periods. These patients have also been on anti-allergic therapy.

There is one group of ten patients in whom small, middle meatal polyps were noted in routine examination. These patients were all allergic. One or two injections into the substance of the polyp were sufficient for retardation of the polyp size. In seven of these, the polyp was seen to disappear from observation. There undoubtedly was a small amount of polyp remaining which was obscured from vision by its position in the meatus.

All of this group have been seen on subsequent occasions when it became necessary to repeat the injections followed by correspondingly good results.

CONCLUSIONS

1. The first approach to obstructive nasal polyps must, of necessity, be surgical.

2. The next step should be one of work-up with adequate anti-allergic therapy.

3. In conjunction with anti-allergic therapy, medicaments of known value and injectable steroid agents should be used.

4. The combination of all these methods of treatment will offer the best results for the patient.

5. Continued search must be made for newer methods of therapy for cases which resist all these combinations.

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COAL FOR COLORS

Secretary for Health, Education, and Welfare, Arthur S. Flemming has transmitted a proposed bill to Congress to establish a new plan of regulation to insure safe use of color additives in foods, drugs, and cosmetics.

The bill would replace the present "coal-tar color" provision in the Federal food and drug law enforced by the Food and Drug Administration.

In transmitting the bill to Congress, Secretary Flemming said that the proposed law would provide a scientifically sound and uniform system for the testing of color additives of any kind which may safely be used in foods, drugs, or cosmetics. When necessary the colors would be subject to appropriate tolerances, limitation, and other conditions of use, and to official testing and certification of individual batches of color so as to insure safety of use to the consumer.

"The theory back of the present law," Mr. Flemming said, "is that some coal-tar colors are so safe that any amount may be consumed, for any length of time, without risk. Modern methods of testing on laboratory animals show this is not true. On the other hand, most of these colors are safe when used in proper amounts. The problem is that the present law does not authorize FDA to limit the amount of color which may be used in foods, drugs, or cosmetics. The Government must ban the use of any coal-tar colors if their use, in large quantities, is harmful, although their use in small quantities may be harmless."

The Secretary said the new bill would expedite the testing of colors to determine safe levels of use by requiring color manufacturers to do the appropriate research and to submit the results to the Food and Drug Administration. All types of color additives would be subject to the safety requirements of the new law, not merely "coal-tar colors" as at present.

THE EFFECTIVENESS OF SCOPOLAMINE N-METHYL BROMIDE (PAMINE BROMIDE®) IN THE TREATMENT OF BRONCHIAL ASTHMA

A Spirometric and Clinical Study

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IN recent years a series of reports concerned with the effectiveness of synthetic anti-cholinergic agents in the treatment of asthma has been forthcoming from many clinics, including our own.[1-9] This paper reports our experience with scopolamine N-methyl bromide, Pamine Bromide®.* As in the cases of other anti-cholinergic drugs, Pamine Bromide was originally introduced into clinical medicine for the management of peptic ulcer and other conditions characterized by gastrointestinal hypertonicity and gastric hyperacidity. Again, as with other drugs in this genre, it has been found to possess considerable effectiveness in the treatment of bronchial asthma.

PHARMACOLOGY

Pamine Bromide® is obtained by the reaction of scopolamine (l-hyoscine) and methyl bromide. Its molecular weight is 398.3. It is soluble at 128 Grams per 100 Grams of water. It is unstable in aqueous solution at pH 8 and above.

The pharmacologic actions have been reported in detail by Visscher and his colleagues.[10] They coincide with those of anti-cholinergic drugs in general. Despite a marked tachycardia produced by the drug in dogs, no such effect has been noted clinically in patients receiving therapeutic doses for the treatment of peptic ulcer. It is of special interest to note that the drug was not notably active as a bronchodilator on the tracheal chain of guinea pigs using a modification of the method of Castillo and deBeer; it was found to be less than one-hundredth as potent as epinephrine in relaxing histamine-induced contractions of the tracheal chain and about one-hundredth as potent as epinephrine against acetylcholine-induced contractions. In a comparative study of several anti-cholinergic substances, Kirsner and Palmer found Pamine Bromide® to be the most potent in suppressing gastric secretion and with proportionately fewer and less distressing side reactions.

From the Department of Therapeutics, New York University-Bellevue Medical Center and the Allergy Clinics of the Beekman-Downtown, Bellevue, and Beth Israel Hospitals, New York City, New York.

*Pamine Bromide® is a product of The Upjohn Company, Kalamazoo, Michigan.

METHOD

The responses of asthmatic patients have been evaluated spirometrically for short-term observations administering the medication intramuscularly and with long-term observation in the clinic using the drug orally.

Spirometric Studies.—The spirometric technique used in the study has been described elsewhere.[12] Summarized briefly, it employs a battery of ventilatory function measurements consisting of the vital capacity following a maximal expiration, the vital capacity following a normal expiration and the maximal breathing capacity. The first method, designated the deep breathing type of maximal breathing capacity (deep MBC) measures ventilation when the patient breathes as deeply and rapidly as possible. The second variant is the rapid maximal breathing capacity (rapid MBC). This is carried out with the patient breathing as rapidly as he can without regard to depth. After the control study which consisted of a minimum of two test runs, 20 minutes apart, Pamine Bromide® was administered intramuscularly in doses of 0.25 mg and the battery of tests was repeated at half-hour intervals, usually over a two-hour period following the administration of the drug.

The apparatus used in this study was the Collens respirometer. This is essentially a Benedict-Roth water-seal apparatus with the additional advantages of a nine liter tank and a two-speed kymograph. The former feature reduces the oxygen dilution factor and the latter increases the legibility and ease of calculation of the tracings, especially in rapid MBC studies.

At the time of testing, patients were classified in one of three categories. Class I included those patients who showed no physical evidence of asthma on auscultation of the chest and who were entirely free of symptoms. Class III asthmatics were those who were tested during the course of an acute episode. Class II patients were those asthmatics who were experiencing "mild" difficulty. These patients either exhibited typical wheezing on auscultation without severe dyspnea or complained of mild to moderate respiratory embarrassment in the absence of physical findings. Most of our patients fell into this last category and described this as their usual status. They would be classified clinically as "mild to moderate" asthma.

Using the technique and method of classification described above, we have carried out spirometric studies on thirty patients. The age distribution ranged from thirteen to sixty-eight and they were equally divided, fifteen males and fifteen females. The results of these studies in each patient are listed in Table I. The great majority of these patients have been tested frequently in the past using other medications. They can be considered as trained subjects; however, we have demonstrated that training does not play a significant role in the reliability of this testing procedure.

The therapeutic responses, graded from 0 to 4, were determined by the

TABLE I. SPIROMETRIC STUDIES ON PAMINE 1.25 MG INTRAMUSCULARLY IN PATIENTS WITH BRONCHIAL ASTHMA

	Patient	Age	Sex	Class of Asthma	Vital Capacity		MBC§ (Deep)		MBC§ (Rapid)		Subjective Response	Side Effects
					Per Cent Change	Grade of Improvement	Per Cent Change	Grade of Improvement	Per Cent Change	Grade of Improvement		
1.	W.C.	60	M	II	12.5	0	43.3	1	25.0	1	Slightly improved	Slight dryness of mouth and throat
2.	C.B.	51	F	II	10.0	0	36.3	1	11.1	0	Much improved	"Dry"
3.	A.S.	16	M	II	41.7	1	40.0	1	15.7	0	"Better"	"Dry"
4.	M.D.	41	M	II	25.3	1	24.0	1	28.3	1	Slightly better	Very dry
5.	J.R.	60	M	II	9.0	0	14.2	0	32.0	1	Much improved	Dry
6.	D.B.	51	F	II	54.5	2	73.9	2	70.0	2	Greatly improved	Slightly dry
7.	F.B.	68	F	II	7.0	0	53.8	2	25.0	1	Improved	Slightly dry
8.	O.U.	50	M	II	19.1	0	27.2	1	94.2	3	Better	Dry
9.	J.F.	42	M	II	16.6	0	37.0	1	12.0	0	No change	Dry
10.	A.C.	58	F	I	8.0	0	15.0	0	30.6	1	Better	Dry
11.	L.Z.	54	F	II	32.6	1	69.7	2	63.3	2	Improved	Dry
12.	P.B.	42	M	II	2.0	0	32.0	1	53.0	2	Improved	Dry
13.	J.M.	44	M	III	73.5	2	101.1	4	0.0	0	Better	Dry
14.	S.T.	31	F	II	0.0	0	4.7	0	0.0	0	No change	Dry
15.	*H.M.	41	M	II	30.4	1	45.0	1	28.2	1	Much improved	Dry
16.	M.S.	13	M	II	54.0	2	53.8	2	93.0	3	Improved	Dry
17.	C.S.	49	F	III	66.6	2	66.6	2	156.0	4	Improved	Dry
18.	*L.F.	15	F	I	1.4	0	39.8	1	80.0	3	Chest better	Dry
19.	P.G.	53	M	II	21.6	1	0.0	0	0.0	0	No change	Slightly dry
20.	C.E.	29	F	II	21.6	1	47.6	1	0.0	0	Improved	Slightly dry
21.	A.E	38	F	II	3.0	0	48.1	1	12.0	0	Moderate improvement	Nausea—Vomited once
22	R.H.	22	F	III	31.2	1	21.6	1	53.3	2	Improved	None
23.	P.H.	67	M	III	22.2	0	12.0	0	34.7	1	Somewhat improved	Dry
24.	C.S.	49	F	II	44.4	1	75.0	2	47.4	1	Improved	Dry
25.	R.S.	46	M	II	40.5	1	58.3	2	50.0	1	Improved	None
26.	E.O.	58	M	II	37.8	1	35.0	1	60.0	2	Slightly improved	Dry
27.	T.M.	15	M	I	10.0	0	11.1	0	33.3	1	Improved	Dry
28.	**E.C.	34	F	III	60.0	2	48.1	1	25.0	1	Improved	Dry
29.	L.P.	45	F	II	5.8	0	0.0	0	13.4	0	Improved	Dry
30.	‡C.E.	28	F	II	6.0	0	26.3	1	25.8	1	Improved	Dry

Key to grade of response:
0— 0-20% 1—21-50% 2—51-75% 3—76-100% 4—101+%

*Intramuscular injection of 0.2 cc epinephrine gave no further improvement.

†Improvement noted despite lack of asthma clinically at time of testing.

**Improvement on pamine after faliure to respond to relaxin intramuscularly given two hours earlier.

‡Further response to pamine after moderate response to relaxin intramuscularly had leveled off.

§Maximal breathing capacity.

changes in vital capacity and in both types of maximal breathing capacity compared with control readings. In our previous studies it was found that changes under 20 per cent in the three basic spirometric variables should be considered within the experimental range, "O" therapeutic

TABLE II. THERAPEUTIC RESPONSE OF PATIENTS WITH BRONCHIAL ASTHMA TO PAMINE (0.25 MG IM)

Grade	Vital Capacity		Maximal (Deep) Breathing		Maximal (Rapid) Breathing	
	No. of Patients	Per Cent Cases	No. of Patients	Per Cent Cases	No. of Patients	Per Cent Cases
0	15	50.0	7	23.3	9	30.0
1	10	30.0	15	50.0	12	40.0
2	5	16.7	7	23.3	5	16.6
3	0	0	0	0	3	10.0
4	0	0	1	3.6	1	3.4

response. Most asthmatics tested following saline injections gave variations of less than 10 per cent from the control levels, but a few ranged just below 20 per cent, which has therefore been designated the upper limit of experimental variation in this study. Increases over the control level of 21-50 per cent are Grade I responses, 51-75 per cent Grade II, 76-100 per cent Grade III, and over 101 per cent Grade IV responses (Table I).

Oral Studies.—Forty-one patients on oral medication were followed for periods ranging from one week to eight months. Patients reported to the clinic usually at one-week intervals, a few returning at two-week intervals. In most instances Pamine Bromide® was alternated with other drugs commonly used in the clinic. Patients were started on 2.5 mg orally, either every four hours for those complaining of persistent symptoms, or as the occasion arose for those experiencing intermittent episodes. Patients were instructed to increase the dose level by 2.5 mg increments until they either secured adequate relief or until mild side effects, usually dryness of mouth, supervened.

RESULTS

Spirometric.—Table I lists the results of spirometric testing in our series of patients. Table II shows the ranges of response according to our system of grading the thirty patients who received Pamine intramuscularly. We have previously collected spirometric data on a large number of asthmatics using three of the basic drugs most commonly prescribed in the treatment of this disease; in our original studies, the therapeutic effects of two dose levels each of ephedrine, epinephrine and aminophylline were observed. The first two drugs were administered intramuscularly and the third intravenously. Each dose level was tested on approximately thirty patients distributed among the three classes of severity of asthma. An over-all compilation of these results is listed in Table III. This data serves as a standard basis for comparison when studying a new agent in

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TABLE III. PER CENT DISTRIBUTION OF LEVELS OF THERAPEUTIC RESPONSE OF FUNCTIONS TESTED

Function Test	Aminophylline 0.25 gm (IV)		Aminophylline 0.5 gm (IV)		Ephedrine Sulfate 25 mg (IM)		Ephedrine Sulfate 50 mg (IM)		Epinephrine 0.25 gm (IM)		Epinephrine 0.5 mg (IM)		Pamine Bromide 0.25 mg (IM)	
	No. of Patients	Per Cent Cases	No. of Patients	Per Cent Cases	No. of Patients	Per Cent Cases	No. of Patients	Per Cent Cases	No. of Patients	Per Cent Cases	No. of Patients	Per Cent Cases	No. of Patients	Per Cent Cases
Vital capacity:														
Grade 0	18	66.6	19	59.3	26	96.3	16	61.5	16	72.7	8	40.0	15	50.0
Grade 1	7	25.9	7	21.9	1	3.7	10	39.5	5	22.7	9	45.0	10	30.3
Grade 2	1	3.7	3	9.4					1	4.6	2	10.0	5	16.7
Grade 3	1	3.7	3	9.4							1	5.0		
Grade 4														
Maximal (deep) breathing:														
Grade 0	10	37.0	9	31.0	18	69.2	11	42.3	6	27.2	3	15.0	7	23.3
Grade 1	11	40.7	15	51.7	7	26.1	8	29.2	12	54.4	11	55.0	15	50.0
Grade 2	5	18.5	4	13.8	1	4.7	6	23.3	1	4.5	1	5.0	7	23.3
Grade 3	1	3.8	1	3.5			1	5.2	2	9.4	2	10.0	0	0.0
Grade 4									1	4.5	3	15.0	1	3.6
Maximal (rapid) breathing:														
Grade 0	9	33.3	9	31.0	18	69.2	8	32.0	8	36.3	5	25.0	9	30.0
Grade 1	11	40.7	15	51.7	5	19.2	11	44.0	9	40.9	7	35.0	12	40.0
Grade 2	2	7.4	4	13.8	1	3.6	6	24.0	1	4.5	4	20.0	5	16.6
Grade 3	4	14.8	1	3.5	2	8.0					3	15.0	3	10.0
Grade 4	1	3.8							4	18.3	1	6.0	1	3.4

Key to grade of response:
0= 0 to 20 per cent. No response.
1= 21 to 50 per cent.
2= 51 to 75 per cent.
3= 76 to 100 per cent.
4=101+ per cent.

the treatment of bronchial asthma. The last column of this table includes the corresponding figures obtained in the present spirometric studies on Pamine Bromide®. Review of this table indicates that Pamine Bromide® in doses of 0.25 mg administered intramuscularly was a more effective bronchodilator than both dose levels of ephedrine sulfate intramuscularly; was equivalent to the 0.25 mg dose of epinephrine intramuscularly, but somewhat inferior in effect to 0.5 mg epinephrine intramuscularly and was approximately equivalent to 0.25 gm and 0.5 gm doses of aminophylline administered intravenously.

As noted in Table I, virtually all patients receiving 0.25 mg doses complained of some dryness of the mouth. The complaints were not severe, but because of this side effect it was felt that it would be practical to limit the testing dose to 0.25 mg. Larger dose levels, such as have been given many times for the treatment of gastrointestinal disorders, would, undoubtedly, have produced a greater bronchodilating effect, but it was decided to limit the testing dose to that producing minimal side effects to avoid distressing reactions which might nullify the beneficial action on the bronchial tree. One patient was nauseated and vomited; the significance of this occurrence cannot be evaluated in this single instance. No significant effects on pulse or blood pressure were seen. In addition, it is noted in Table I that in two cases patients reacted favorably to Pamine after an initial period of failure to show improvement with another agent under study. In one case, the addition of epinephrine following maximum improvement with Pamine afforded no further relief (an epinephrine "clearance" test which is being studied at the present time). Another patient (No. 18) showed marked improvement on Pamine Bromide® spirometrically despite the clinical absence of asthma at the time of testing. Such responses by Class I patients are not uncommon and indicate that stress testing as represented by the maximal breathing capacity, particularly, is a more sensitive index of the patient's ventilatory function than is his own estimate made at a time when he is at rest.

Oral Studies.—Forty-one patients were followed on oral trials. Table IV lists the clinical details. It is noted that most patients found that 5.0 mg was adequate to secure relief. One patient tolerated 12.5 mg for a period without significant side effects. Attaining the proper dose is of great importance with the use of Pamine Bromide®; in some instances, patients obtained no relief on 2.5 mg, had an excellent response on 5.0 mg, and experienced annoying side effects on 7.5 mg, indicating a narrow therapeutic range in these cases. Some of the failures can be attributed to the patient's reluctance to attempt larger doses after having been disappointed with the initial dose level recommended.

It is noted that a substantial number of patients showed varying responses to the medication; for example, a patient may have responded

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TABLE IV. EFFECTIVENESS OF ORAL ADMINISTRATION OF PAMINE TO PATIENTS WITH BRONCHIAL ASTHMA

Patient	Age	Sex	Dosage	Duration	Therapeutic Effect	Comparison with Other Medications	Side Effects	Comments	Response to Placebo	Response to 26B (Pamine-Reserpine 1 tab q.i.d.)	Response to 25B (Pamine-Phenobarbital 1 tab q.i.d.)
F.B.	60	F	2.5 mg p.r.n.	3 months	Moderate to good	Better than theophylline	None	Relief lasted 3-4 hrs—15-20 mins onset		Moderate to good (4 mos) Same as Pamine alone. No toxicity	
W.C.	60	M	2.5 mg q.i.d.	3 months intermittently	Slight to none	Preferred benadryl and ephedrine	None	Poor response to all medication—severe chronic asthma			Poor response. Complained of nasal stuffiness and dry throat (1 month)
M.G.	71	M	5.0 mg t.i.d.	2 weeks	No relief to slight relief	Inferior to aminophylline which, however, gave slight relief	Took only 2-3 doses because of dryness of mouth	Severe asthmatic. Poor response to all therapy	None		
A.G.	52	M	5-10 mg q4h, p.r.n.	1 month	Good relief		None	Relief lasted 3-4 hrs			
A.McG.	41	M	2.5-7.5 mg q4h p.r.n.	2 months	Moderate relief	Superior to theophylline	None	No response to 2.5 mg. Moderate relief on 5.0-7.5 mg	None to slight (3 tabs q.i.d.)		Slight to moderate relief (5.0 mg of Pamine)
J.M.	44	M	2.5 mg q.i.d.	2 weeks	None to excellent	Poor response to all medication	None	Cor pulmonale. Chronic pulmonary disease accounting for varying response to drug			
A.M.	54	M	2.5-7.5 mg p.r.n.	8 months intermittently	Excellent	"Best medicine he ever took"	None	No tolerance developed over long period	Switched to placebo several times with usual loss of effect immediately or within one week		
M.S.	13	M	2.5-7.5 mg p.r.n.	1 month	Moderate to good	Slightly inferior to various theophylline preparations	None	Good results lasting 4 hrs to all day			
R.H.	22	F	7.5 mg t.i d.	2 months	Moderate		None	Loss of effect at end of period as asthma became increasingly severe			
P.R.	42	M	7.5 mg q.i.d.	3 weeks	Slight to moderate	Inferior to ephedrine and ephedrine-benadryl combination	None				
A.S.	64	M	2.5 mg q.i.d.	1 week	None	Fair response to ephedrine and theophylline drugs	None	Long standing, severe asthmatic	None		Slight response over one week period—also on benadryl

TABLE IV. EFFECTIVENESS OF ORAL ADMINISTRATION OF PAMINE TO PATIENTS WITH BRONCHIAL ASTHMA—CONTINUED

Patient	Age	Sex	Dosage	Duration	Therapeutic Effect	Comparison with Other Medications	Side Effects	Comments	Response to Placebo	Response to 26B (Pamine-Reserpine 1 tab q.i.d.)	Response to 25B (Pamine-Phenobarbital 1 tab q.i.d.)
E.S.	77	F	5.0 mg q.i.d.	3 weeks	Good	"Best yet." Superior to theophylline and theophylline-ephedrine combination	None				
S.T.	31	F	5.0 mg t.i.d.	3 weeks	None	Responded fairly well to aminophylline	None				
C.S.	49	F	2.5-10.0 mg q.i.d.	2 months	Fair relief to none	Ephedrine sulfate "best medication gave only fair relief." Pamine superior to theophylline and antihistamine	Mouth dryness on 10 mg	Very severe asthmatic		Slight relief (2.5 mg of Pamine only)	Slight relief (2.5 mg of Pamine only)
C.V.	28	F	2.5-7.5 mg q.i.d.	Intermittent over 2 months	Slight to moderate	Response fair to slight to variety of medications	None	Response to drug varied with severity of asthmatic episode			No response
D.B.	50	F	2.5-7.5 mg q.i.d.	2 months	Good relief. Lost effectiveness at end of period with onset of bronchitis	"Best yet." Able to reduce frequency of epinephrine injections	None				
E.C.	32	F	5.0 mg q.i.d.	3 weeks	Good relief	Equivalent to theophylline and ephedrine-theophylline preparation	Dryness of mouth became annoying at end of period forcing discontinuance	Moderately severe asthmatic			No response
A.C.	22	M	2.5-12.5 mg q.i.d. to b.i.d.	2 weeks	None	Fair response to theophylline derivative	Slight dryness of mouth	Experimented with varying dose levels—all ineffectual			
J.L.	16	F	2.5-12.5 mg q.i.d.	8 weeks	Poor to slight relief	Responded poorly to all medication—only response to antihistamine—only fair to theophylline combination	Dryness of mouth on larger dose			Fair response	
R.P.	58	F	2.5 mg q.i.d.	2 weeks	None to slight	Fair but varying response to theophylline compounds	Dryness of mouth	Poor response to all oral therapy. Frequent use of (IM) epinephrine		None	None

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TABLE IV. EFFECTIVENESS OF ORAL ADMINISTRATION OF PAMINE TO PATIENTS WITH BRONCHIAL ASTHMA—CONTINUED

Patient	Age	Sex	Dosage	Duration	Therapeutic Effect	Comparison with Other Medications	Side Effects	Comments	Response to Placebo	Response to 26B (Pamine-Reserpine 1 tab q.i.d.)	Response to 25B (Pamine-Phenobarbital 1 tab q.i.d.)
N.P.	35	F	2.5 mg t.i.d. and p.r.n.	8 months	Excellent	Superior to all other medications	None	Infrequent asthmatic episodes in last several months—readily controlled by 5.0 mg of Pamine	Equivocal responses on different occasions		
A.S.	46	F	2.5-5.0 mg q.i.d	2 weeks	Poor	Responded slightly to theophylline derivative	None				
I.S.	36	M	5.0 mg p.r.n.	3 weeks	Poor to slight	Inferior to ephedrine	None	Severe asthma at period of testing Poor response to most medications			
L.Z.	53	F	5.0 mg p.r.n.	3 weeks	Moderate	Equivalent to aminophylline	Slight oral dryness	Chiefly early AM attacks—relieved by Pamine for remainder of day			
R.A.	65	F	2.5 mg t.i.d.	7 weeks	Fair to good		Slight oral dryness		None		
M.B.	48	F	2.5-5.0 mg p.r.n.	2 weeks	None	Inferior to ephedrine-aminophylline combination	Slight nausea				
R.F.	39	F	5.0-7.5 mg p.r.n. to q.i.d.	3 months	Fair	Superior to various theophylline and theophylline-ephedrine combinations	Mouth dry on 7.5 mg—not on 5.0 mg	On prednisone in addition, but still had frequent periods of wheezing	None		
M.F.	54	F	2.5-5.0 mg	1 week	Fair to good		None				
F.F.	67	F	2.5 mg p.r.n. to q.i.d.	2 weeks	None	Inferior to aminophylline suppositories. Poor response to ephedrine	None	Small doses of Pamine used	Fair to moderate		
I.G.	3½	M	1.25 mg	1 week	None	Poor response to all therapy	None	Severe case of infectious asthma			
S.H.	50	M	2.5 mg q.i.d.	1 week	None		None				
A.K.	65	F	5.0 mg q.i.d.	2 weeks	Slight	Poor response to all therapy, including prednisone therapy	None	Very severe asthmatic. Frequent visitor to emergency room. Skin nephrosis from overdose of epinephrine	Slight response. Unable to differentiate placebo from drug.	None	

TABLE IV. EFFECTIVENESS OF ORAL ADMINISTRATION OF PAMINE TO PATIENTS WITH BRONCHIAL ASTHMA—CONCLUDED

Patient	Age	Sex	Dosage	Duration	Therapeutic Effect	Comparison with Other Medications	Side Effects	Comments	Response to Placebo	Response to 26B (Pamine-Reserpine 1 tab q.i.d.)	Response to 25B (Pamine-Phenobarbital 1 tab q.i.d.)
Ad.K.	60	M	2.5-5.0 mg q.i.d.	4 months	Excellent	Superior to ephedrine aminophylline combination	Slight dryness of mouth	Moderately severe asthmatic	Slight response initially—quickly "lost effect" with rapid response when drug administered	Good. Preferred Pamine alone	Fair
B.L	30	F	5.0 mg q.i.d	6 weeks	Good for mild wheezing; poor for severe episode	Equivalent to aminophylline					
C.P.	28	F	2.5-5.0 mg p.r.n. to q.i.d.	2 weeks	None	Inferior to theophylline-ephedrine combination	None		None to slight		
A.S.	60	M	2.5 mg p.r.n.	2 weeks	None	Poor response to all therapy, except for slight response to aminophylline suppositories	Tinnitus. Hands itch				
L.S.	9	F	2.5 mg p.r.n.	6 weeks	Excellent and prompt response to spontaneous episodes—poor when asthma associated with URI	"Best yet"	None				
R.W.	48	F	2.5 mg p.r.n.	2 weeks	Excellent	Superior to antihistamine	Belching and heartburn occasionally		Slight response		
R.T.	32	F	5.0-7.5 mg p.r.n	5 months	Excellent in most episodes—poor during period of URI	Superior to all standard medications	Slight oral dryness occasionally		Slight response initially—later none. Excellent response when Pamine resumed		
B.S.	65	M	5.0 mg q.i.d.	2 weeks	Very moderate—"cough relieved"	Good response only to prednisone	None	Case of infectious asthma			
J.R.	54	M	5.0-7.5 mg p.r.n.	7 months	Excellent	Superior to all other medications	Mild dryness of mouth	On cortisone 25-50 mg o.d. for 2 years	On placebo 3 times during period of testing. Noted definite "lessening" of effect in 1-3 weeks with immediate increased response when drug resumed		

well for one or more weeks and later reported a diminution or absence of effect. Such variability of response, which probably depends on the development of drug tolerance or a spontaneous worsening of the asthmatic state, is well known to clinicians. In addition, many other factors may play a role, such as the development of respiratory infections, variations in atmospheric conditions, use of other drugs, and so on. Such variations make the evaluation of therapeutic response to any anti-asthmatic agent difficult. We have used the maximal response to therapy as the arbitrary listing in the table if the period of response was adequate in quality and duration. Using these criteria, 60.9 per cent of the forty-one patients responded adequately to oral therapy; twelve patients (29.2 per cent) showed excellent results and thirteen patients (31.7 per cent) received moderate relief. Six patients had only slight relief and ten had no response at all.

Fourteen patients on Pamine Bromide® alternated with placebos of similar appearance were observed. In seven cases there was a good response to the drug and none to slight response to the placebo. In four cases there was no response to placebo or drug. One patient was unable to differentiate between the placebo and the drug and reported fair responses to both. In one instance the patient responded to the placebo and reported no relief from the medication. The over-all picture would indicate a very satisfactory differential between the drug and the placebo. It should be pointed out that the patient was sometimes unable to detect a significant difference between drug and placebo during the first week he was placed on the placebo, after he had already exhibited an adequate response to Pamine Bromide®. He usually appeared uncertain and reluctant to dismiss a medication which had previously given welcome relief. By the second or third week, however, he would usually report that the drug had "stopped working" or that he "had gotten used to it." A return to the use of Pamine Bromide® without his knowledge in such cases invariably brought a report of immediate relief. From our experiences in this and other instances we have concluded that in a disease state as chronic and fluctuating in severity as bronchial asthma, a placebo should be used for periods up to three to four weeks when necessary to determine whether or not a significant difference of response exists between it and the active drug.

As noted in Table IV, comparison of responses to Pamine with responses to other standard medications used in asthma indicated, when a clear-cut report was available, that thirteen patients found Pamine Bromide® inferior to various theophylline preparations, thirteen reported Pamine superior to theophylline (and in several instances "the best yet") and three patients reported similar responses to both Pamine and theophylline. Three patients found ephedrine or other medications (excluding theophylline) superior to Pamine.

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DISCUSSION

In recent years attention has been directed to the role of anticholinergic drugs in the treatment of bronchial asthma. The theories of Eppinger and Hess[13] regarding asthma and other clinical disorders as examples of "pathological vagotonia" are well known. The use of atropine in asthma likewise was well known to older generations of clinicians, but this drug eventually fell into disrepute since the resultant inspissation of bronchial secretions often led to dangerous complications and even death on occasion.[14-16] Nonetheless, the very evident broncho-dilating properties of atropine in the experimental animal and the isolated lung preparation are familiar to pharmacologists. Hence, the search has continued for parasympatholytic agents that might exert an anticholinergic effect on bronchospasm coupled with a less detrimental effect on bronchial secretions.[5,6,17,18] It is interesting to note that Beakey and his associates[6] have stated in the past that "the wet, sweating hypotensive asthmatic patient who may be exhibiting a systemic picture of parasympathetic stimulation (pathological vagotonia) is almost completely resistant to ordinary methods of treatment. It is possible that *hyoscine, hyoscyamine or a derivative* (the italics are ours) may exhibit sufficient sedation as well as broncho-spasmolytic properties that its use might be indicated in spite of its drying action."

Previous studies have amply documented the bronchodilating values of various anti-cholinergic drugs, including di-phenethinylmethyl sulfate (Prantal®),[7-8] methantheline Bromide (Banthine®),[1] and diethyl-(2-hydroxy-ethyl) methylenamine Bromide (Antrenyl®).[3] A recent report confirms our favorable experience with Prantal®.[9]

Salomon *et al*[4] reported their experience with Pamine used as an aerosol. Sixty-eight patients were given aerosols of 0.33 mgm dissolved in one cc of saline. The average improvement in vital capacity was 19.8 per cent and in the maximal breathing capacity, 29.3 per cent. These responses were less in magnitude than those produced by adrenergic bronchodilators aerosols, particularly isopropylarterenol (Isuprel®). The authors suggest, however, the possible use of anti-cholinergic drugs in patients refractory to adrenergic agents and point out the value of Pamine in patients with hypertension and cardiovascular disease or tachycardia. Five patients were protected by Pamine against methocholine. Eighteen patients used the aerosols at home and obtained adequate relief.

Pamine has been a very satisfactory agent in our hands and our observations would indicate that it has a place in the therapeusis of bronchial asthma by both the oral and the parenteral routes. Administered parenterally, it has a high degree of predictability and ranks favorably with the established medications used in bronchial asthma. Given orally it has a fair predictability of response again ranking well with other agents used in the treatment of chronic asthma. By either route the side effects are not significant and do not deter the use of the drug. The absence of significant effects on blood pressure and pulse enhances the safety of Pamine in the

cardiac patient. Because of the absence of myocardial irritation inherent in drugs such as epinephrine or ephedrine, it is suggested that Pamine and other bronchodilating anti-cholingergic drugs might have a place in the control of the occasional case of asthma that arises during deep anesthesia, although such studies have not yet been carried out, to our knowledge.

The occasional dryness of the mouth resulting from persistent oral usage is not marked and only infrequently resulted in reluctance to continue the medication. Certainly the side effects are less distressing than those frequently resulting from the oral administration of theophylline compounds or ephedrine. Barach and Bickerman[19] caution against the continued use of anti-cholinergic agents in the treatment of patients with "retained secretions who appear to have difficulty in raising thick, tenacious sputum. The 'wet' asthmatic or emphysematous subject with bronchorrhea would be benefited most by this drying action." We have not noted any problems of this nature in our series and many patients have now been on Pamine for a year or more. As with all anti-cholinergic drugs, special caution is urged in the older age group, where the possibility of precipitating glaucoma exists. To date we have seen no complications of this type.

It is worthwhile to point out again the disparity between the very favorable clinical behavior of the drug with the unimpressive results obtained on the tracheal chain of guinea pigs by the method of Castillo and deBeer. This is further evidence, if such were needed, that the final test—and the only really valid one—of an anti-asthmatic agent must be made in the human subject under routine clinical conditions.

In a previous report we stated that ". . . the use of anti-cholinergic drugs basically possesses considerable merit in the treatment of bronchial asthma. A further study of such compounds in the treatment of this disease is indicated. It is possible that synthesis of other anticholinergic substances may in the future provide drugs which will have a more specific effect upon the bronchial mucosa while at the same time minimizing or reducing the toxic and unpleasant side effects associated with anti-cholinergic compounds at this time. It is realized, of course, that no basic conclusions regarding the mechanism or etiology of asthma, particularly with reference to chemical medication, can be drawn from this study." Our experience with Pamine Bromide® has not caused any change in these opinions.

CONCLUSIONS

1. The spirometric study of Pamine Bromide® administered intramuscularly in doses of 0.25 mg to thirty patients indicates that this drug is a potent bronchodilator.

2. Pamine by the intramuscular route was superior to both 25 mg or 50 mg of ephedrine sulfate given intramuscularly, approximately the equivalent of 0.25 gm and 0.5 gm of aminophylline given intravenously, was equal in effectiveness with 0.25 mg of epinephrine administered intamuscu-

larly, but somewhat inferior to 0.5 mg of epinephrine given intramuscularly.

3. Pamine was effective orally in 60.9 per cent of forty-one asthmatic patients. The average effective dose was 5.0 mg. given at four-hour intervals.

4. Side effects by the oral and the parenteral routes consisted chiefly of mild to moderate drying of the mouth. No cardiac or ocular complications were noted.

5. The further study of anti-cholinergic agents in the treatment of bronchial asthma is indicated.

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PSEUDOALLERGIC SCHIZOPHRENIA

A New Clinical Entity

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THERE IS an important group of patients who present allergic symptoms referable to the many tissues of the body, but this group is characterized by the following diagnostic difficulty: the usual relationship between allergen and reactive tissue is either not readily determined or impossible to discover. Numerous non-immunologic devices have been employed to keep these patients within the frame of reference of purely immunologic allergy rather than to recognize the importance of nervous or psychologic forces. For example, an increased pulse rate following ingestion of certain foods has been used to label foods as allergenic. The physicians employing pulse rate to diagnose allergy, for example, apparently have not adequately recognized the role of anxiety in tests of this type and, therefore, have not performed appropriate control tests to establish psychiatric diagnoses in these patients.

In 1949, an important general advance toward the special understanding of many patients with allergic symptoms was made by Hoch and Polatin.[1,2] They described pseudoneurotic forms of schizophrenia and called attention to those patients who clinically demonstrated symptoms which hitherto have been considered by many psychiatrists to be psychoneurotic. However, these patients did not usually deteriorate in the way that schizophrenics may, and they had no hallucinations or delusions. Careful investigation of these patients heretofore considered neurotic, however, revealed clinical symptomatology very similar to that seen in schizophrenia. Hoch and his co-workers in follow-up studies described a number of these patients as having had short psychotic episodes. Others became frankly schizophrenic. In a more recent paper, Hoch discusses his research dealing with individuals having the psychotic structure of schizophrenia but not suffering gross psychotic symptoms. His approach consists of an analysis of the clinical manifestations of patients suffering from pseudoneurotic schizophrenia and the investigation of alterations in the physiological functions of schizophrenic patients with a view to integrating the functions of "mind and brain." Hoch summarizes and distinguishes clearly between the primary symptoms of schizophrenia and those of pseudoneurotic schizophrenia in this important paper.

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The purpose of this study is to present the first of a series of cases of pseudoallergic schizophrenia. This new classification is derived from the studies of Hoch and his colleagues on pseudoneurotic schizophrenia. Essentially, the patient suffering from pseudoallergic schizophrenia uses the allergic symptomatology (both preconsciously and unconsciously) as a mechanism designed to avoid dealing with his psychotic process. Numerous and diverse rationalizations are made especially plausible by a medical diagnosis of allergy and the support given by the physician's treatment for an allergic illness. The first case is presented in detail not only because it is the first of the series to be reported, but also because the author was fortunate enough to have a verbatim recording of the initial interview as well as the follow-up during hospitalizations in mental institutions.

Case 1.—The following case report begins with verbatim recordings of two interviews with the patient, a twenty-year-old single girl. At the first interview her mother was also present. The patient was referred by an allergist as a "psychosomatic" problem. When the patient drew out of her purse a list of her symptoms and proceeded to enumerate a long list of allergic symptoms referable to nearly every organ in the body, she was informed that her history was extremely important and that it would be better if it were recorded. Since she interposed no objection, complete recordings of the two initial interviews were made. After the second visit, the patient agreed to psychiatric therapy.

Interview with Patient and Her Mother

Patient: I remember distinctly before my attack of bronchial pneumonia, whenever I went in swimming or whenever I took a bath, I felt this terrible pressure on me, even when I was about eight or nine years old. And he (a doctor) said I couldn't remember back that far, but I remember! I have a very good memory for that! My mother will tell you certain things that I remember and I didn't think much of it at the time. I thought it was absolutely normal for everyone to have that pressure on them. It was on my chest sort of, just over my chest and on my head also.

There's something I forgot to mention. For a number of years I have a little pimple over here (neck); it was filled with blood and if I cut the pimple or anything, it bled, but it grew back again. Just about a year ago it went away after I had been on a very good diet without any sweets, and I had been taking a very high potency of vitamins, and it went away by itself and I haven't been bothered by it since. I don't know what else to say. Shall I just say anything?

Doctor: Yes, talk about anything you want to. Look through your own notes to see what are the most important symptoms. What would you say are the most important symptoms you have now?

Patient: Well, there's the palpitation of the heart. Another thing funny about it was that this last time I had an attack and I didn't take any penicillin and the attack wasn't severe at all. And, I also read an article about if you have a fungus infection on your foot it had something to do with your taking penicillin and it bringing on allergic attacks. I didn't take the penicillin and I didn't have a bad attack.

My eyes always itch whenever it rains and I feel very sick at the seashore; very bad. And at the mountains where the air is lighter I feel very, very good.

I always get the swollen glands right over here and over here, throughout my neck.

Doctor: When do you get the swollen glands?

Patient: Usually at the beginning of the attack for a few days.

Doctor: What kind of an attack is this?

Patient: It's very strange. I can explain it this way: you take a parenthesis and it's all inside that parenthesis; starts out very lightly and it gets worse and worse, and it gets deeper and deeper and more complicated, 'til it reaches like a crisis or

something and then just diminishes. But I'm very happy that my last attack wasn't bad at all.

Doctor: Well, would you mind describing a severe attack for me.

Patient: Well, I get palpitations of the heart and they'd be so bad that I can't leave my bed without gasping for breath. And I can just feel as though my heart were popping out of my skin, it beats so strongly. And I get soreness, I can hardly talk for minutes at a time.

Doctor: Where is the soreness?

Patient: It's in my throat, and a funny thing, it's in my palate, and there's a spot on my palate and that bothers me. But even most important is the chest symptom. I get this pressure and heaviness on my chest and I have a terrible headache, which I have now; it's pressure on my head. It's a hot headache. It's on my eyes. And I usually relieve it by just putting my cold fingers there which alleviates it.

Doctor: Let's talk about your chest symptoms. What happens?

Patient: Well, I have sort of like a muscular contraction on my heart, and I don't know if you believe this or not, but no one ever believes me when I talk about this; there's sort of like a muscle leading to my toe and it sort of contracts the muscle in my large toe, my second toe, they just sort of get together like this, very tight, and I just have to sort of uncontract them or something.

Doctor: And do you have this feeling when you have this heaviness in your chest?

Patient: Yes. And I have a muscular contraction in my armpit and my eyes swell.

Doctor: Do you have any wheezing in your chest; do you have whistling; do you have asthma?

Patient: That's very strange. I had a sort of congested feeling; I don't know if I'm explaining it right, but sometimes across here, the topmost part of my chest, and it feels as though I couldn't get enough air through my lungs or something, and it feels somewhat congested. I don't know if I'm explaining it correctly, but it's congested.

Doctor: Go right ahead; you're doing very well. Do you have any difficulty in getting your breath out?

Patient: No.

Doctor: Do you have any wheezing in your chest?

Patient: What do you mean by that?

Doctor: Wheezing, whistles, does your daughter have whistles in her chest?

Mother: No.

Doctor: Or sneezing?

Mother: No. she belches a lot.

Patient: Yes, I belch an awful lot; I hiccup a lot, too.

Doctor: Now, some of these symptoms, I gather, could be allergic.

Patient: Yes, I was tested. Didn't I tell you about that?

Doctor: No, you didn't tell me about that.

Patient: I was tested for allergic symptoms and found out I was allergic to dust. I only had ten tests. I wasn't allergic to pollen or dander, or ragweed or feathers or anything like that, but I was allergic to dust, and I'm sure some foods bother me.

Doctor: When you say ten tests, do you mean ten visits?

Patient: Just ten tests.

Doctor: Ten scratch tests?

Patient: Ten scratch tests. And I've taken Pyribenzamine. They don't help me. they just get me drowsy. I did take some nose drops; they helped me, and I have a bad sinus condition. I've had that for a few years. I have pains in my stomach sometimes. This happened about a year ago. Lately the attack hasn't been as bad as this. My body always trembles, my hands shake, my whole body trembles. I feel very weak and dizzy all the time. And I get very depressed and very moody when I'm in the attack, very excitable, and I feel completely exhausted in my arms and legs. (Mother trying to say something, but patient speaks "over" her.) I hope I don't sound like a hypocondriac; I'm trying to be very precise about this. I'm just trying to write down everything that's happened.

Doctor: Well, you tell me everything.

Patient: It sounds so much.

Doctor: Well, it is quite a bit, but you have those feelings, don't you?

Patient: Yes.

Doctor: Well, these are really your feelings and we must consider your case from that point of view. Certainly if your throat itches that could be an allergic reaction, couldn't it?

Patient: Yes.

Doctor: And if you have heaviness in your chest, that also could be an allergic reaction.

Patient: But I've had that since I was very young, since I was about five or six years old, I remember that. And I never mentioned it.

Mother: And let us say before the attack she had pneumonia and she went bathing once and something happened in the water.

Patient: Oh, I forgot to tell you, somebody pushed me into the water.

Doctor: When did that happen?

Patient: That happened when I was about eight years old.

Doctor: Would you mind telling me about that?

Patient: I can tell you.

Mother: Well, she didn't tell me, doctor, after she had been to the doctor. Always before that happened she loved water, but after a while I see she doesn't like to go near the water. And every time she goes near the water her body shakes. So, I tried to ask the doctor to find out what's the reason for that. She told me about the time that somebody pushed her in the water, and I think it must be something. It frightened her or something.

Patient: No.

Doctor: How old was your daughter when that happened?

Patient: But that doesn't bother me. I went into water after that and it didn't bother me at all; and after that I went swimming. That didn't bother me, because I remember this from a long time ago. Whenever I used to go swimming it was very hard for me to catch my breath in the water. And I thought that I was just short of breath. I've heard a lot of people get that in the water, so, I didn't think much about that. But I remember since I've had these symptoms, I found out I had an allergic basis. I remember when I was six or seven years old, whenever I used to take a bath I used to feel this pressure in the bathtub. I don't know about rainy weather; rainy weather didn't both me. Also when I went swimming, I remember the same thing. This was before that incident; it didn't bother me that somebody pushed me into the water.

Doctor: This started when you were about eight, I believe, this feeling in your chest?

Patient: Yes, even before that. I never mentioned it to anybody.

Doctor: What other allergic symptoms do you have?

Patient: My eyes swell; they itch; they're red and my nose swells and there's mucus in the morning; I have a sort of a sour stomach. I used to have a lot of boils but I think I used to be on a very bad diet. I have pimples on my face; I don't know why, because my diet is very good now. I have a lot of vitamins and I eat a lot of meat. And the diet is so good I can't see why my skin should break out. I have pressure on this temple over here, and sometimes on this side, but mostly on this side.

Doctor: Does your skin ever break out with hives?

Patient: No.

Doctor: Do you have any itching on your skin?

Patient: Sometimes I get it on my hands, but very rarely. I get twitching all over my body and like worms crawling. I menstruate very badly. I menstruate at two to three week intervals and they last from six to seven days.

Doctor: What are you doing now; are you at school?

Patient: Now I'm not doing anything. I feel very frustrated because I want to be a writer and I've written some things and my teacher says they're good and she wants me to send them away. I haven't been able to type them. And I was looking for a job; I haven't worked for some time now. I was looking for a job and I wasn't able to get one. And that's bothering me, too.

Doctor: Has there been any sudden change in your feelings, do you think these are all getting worse, or is this pretty stationary?

Patient: The attacks?

Doctor: Yes.

Patient: I think they're getting better; I'm improving. My condition is improving because it wasn't as severe. I don't understand, because I didn't take any penicillin for it. And the attack itself wasn't serious, and, of course, there wasn't any household friction.

Doctor: Tell me about the household friction, or would you rather not in the presence of your mother?

Patient: Well, there really isn't much to tell, ordinary family arguments; I mean I'm really oversensitive to that and I suppose it does bother me.

Doctor: Family arguments?

Patient: Yes (laughing nervously), well, I prefer weekdays more because nobody is in the house; and, well, weekends come along, everyone is home; even when it's quiet I always feel the next moment is going to bring an argument. And I guess I'm a little tense on account of that.

Doctor: Does it embarrass you to talk about this in front of your mother?

Patient: I suppose it does a little bit.

Doctor: Suppose we finish this visit tomorrow, without your mother. Would you mind that Mrs. X?

Mother: No, surely not.

The second interview was held the next day. The following excerpts from the interview disclose a pattern similar to that found in the initial interview.

Excerpts from the Second Interview

Excerpt 1

Patient: Well, I know this much, whenever I get very excited or irritable—I know I can get an attack that way, even if I'm not overeating or if it isn't raining. I know that. I have dreams at night, if that's anything.

Doctor: Well, what are your dreams like?

Patient: I don't remember. Sometimes I remember, but they don't make sense to me anyhow so I forget about them.

Doctor: Are they nightmarish? Are you bothered, or are they fun?

Patient: Yes, slightly on the nightmarish side sometimes. I used to have—I don't know, if I say this you'll probably think that everything is psychological, and I'm sure it isn't. I used to have dreams about water; that's probably because I realize that I'm allergic to water. I used to have dreams that there were waves coming over me or something like that. Maybe you'd better ask me some questions.

Doctor: Well, how did you happen to get the idea that you're allergic?

Patient: Well, I found out that the symptoms coincide with a person who has allergic symptoms. And I was wondering—I read some books on colds; I thought it was just a chest cold or head cold that I was having, with a sore throat, and I found out some of the things that I've had, this palpitation of the heart, that wasn't normal with a cold. So, I read some books and I listened to the radio, to people talking about that too, and I just found out it was an allergy. I wasn't sure till a year ago, till I was tested.

Doctor: Tell me about the doctor you saw a year ago when you were tested. Was it Doctor Y?

Patient: I just went to him recently.

Doctor: Who was the first doctor you went to?

Patient: This doctor I went to was a Doctor X. He's not a specialist—and he found out—he took a blood chemistry, and he found out I had a gallbladder condition, and he told me to see this other doctor, Doctor Y, and have some skin tests made, and I just had ten tests and I found out I was allergic to dust. My mother discontinued the tests. She's been telling me all these years it isn't an allergy; she still doesn't want to believe it. It's probably too hard for her to believe in some way; or maybe she doesn't feel she wants to sympathize with me.

Excerpt 2

Patient: Well, I'll be perfectly honest and frank with you, I ran away from home twice. The first time was with my sister. We took what we had out of the bank and we went to California. It was the farthest away—to get as far as possible. That didn't prove to be successful and we had to come home. And I went away myself the second time, and that wasn't successful either—I think I would have done it another time if I wasn't so sick.

Doctor: When did you run away from home the first time?

Patient: That was 1948. I know I had just gotten over one of these attacks, in fact, I wasn't even over it and I wanted to leave. And on the train—my father bought me a box of candy and I ate most of it, and I usually get a very bad sore throat from that. It wasn't as bad as it usually was, but I did have a slight cold; a funny thing, when I got to California I had a slight cold, but it didn't develop into an allergic attack. Nothing happened while we were there; we were there for about two and a half months.

Doctor: What sort of an allergic attack did you expect in 1948 in California?

Patient: What do you mean, the attack I usually get?

Doctor: What then happened at that time? I'm trying to ascertain if this was really an allergic attack. I wonder what you would have called an allergic attack in 1948.

Patient: Well, if I couldn't breathe, if I had palpitations of the heart, get the pressure all over my body, mostly in my chest, and pressure in my head, sore throat, and various pains in my back, and fever, weakness, dizziness, exhaustion, insomnia at times, and that's the attack. And these symptoms are sometimes so severe that I'm unable to leave my bed, I just have to be in bed all day. My mother can't understand that. This has been going on for six years, and she never believed that I was really sick. She didn't believe that I was sick at all. She thought I was just making-believe. And I still stay in the room and I have the lights off, because the lights hurt my eyes. And I even pull the window shades down, because I feel more restful that way. And my mother is always coming in the room with my father, and they pull the window shades up and say to get out of bed, and put the lights on. They don't like me to stay in a dark room. My father is a little afraid of the dark, I think, so he thinks that I might be afraid of it too, but I feel much more restful that way. But they don't like that; they always say, "Get out of bed and go down and get some fresh air," which there isn't much fresh air in New York anyhow. Well, what was I trying to say—well, both the times were unsuccessful.

Excerpt 3

Patient: I don't know. I think I'm allergic to certain foods and to rain and to water.

Doctor: Allergic to rain—weather changes do produce allergic symptoms, but what do you mean by being allergic to water?

Patient: I know it sounds strange, but every time I take a bath, or even if I just take a towel—not my hands or my face, because I've washed my hands and my face for so many years, you know, but my feet or any other part of my body—even with a towel—it produces some effect and palpitation of the heart, and I can't breathe and it's hard for me to catch my breath. And when I take a bath, it is sometimes unbearable and that starts an attack. I feel the pressure coming in on me when I'm in the water, or swimming; I feel the shortness of breath and I feel the pressure on my chest.

Doctor: What happened in California when you took a bath?

Patient: I don't think I really took a bath. I was really afraid to. I so rarely take a bath now. I hate to admit it. I mean, I just wash myself.

Doctor: Well, didn't you wash in California?

Patient: I took a sponge bath, it didn't bother me so much. I suppose when my mind was occupied with other things—and I know generally when actually a person feels happy they don't feel sick. So I suppose I'm not happy at home; it isn't only me, my sister isn't either. And she's probably heading for a nervous breakdown. I'm glad I'm not in her shoes because she's twenty-five years old and she's very nervous and very irritable. I mean, I can do things more calmly than she.

Excerpt 4

Patient: I used to be very enthusiastic, very bright, more alert than I am now, very perceptive—I'm just being objective, I'm not being conceited—but people told me this. I was bright, I was skipped a few times in school, and I had very high grades. I would say I was very friendly, but I would say I was very hard to get to know. I suppose I was a little shy at first. But I got over that although I was very, very shy. But I got over that because I used to make myself do things I didn't want to do. Such as, I was ashamed sometimes to answer in class, and talk up in front of a lot of people; but I used to make myself do it because I knew that would be good for me, otherwise I would get into a shell. I would say I've changed, I mean, because I've been through a lot, being sick and in bed; it's years now, and I don't get around much; I've missed a lot.

Doctor: How much have you stayed in bed?

Patient: Well, the attacks have been getting worse and worse, like this last year I've stayed in bed about nine months out of the past year.

Doctor: Nine months? And who took care of you?

Patient: I took care of myself; I got up from bed and made my own food.

Doctor: Did you make your own bed?

Patient: Yes.

Doctor: Keep the room clean?

Patient: Well, I wasn't able to do much of that because I get exhausted very easily and when I feel fatigued the attack is more severe. My mother tried her best to—she isn't in the house all the time.

Discussion of Case 1.—The symptoms in the preceding history which could be allergic in origin may be enumerated from the first visit as: (1) Discomfort on swimming, (2) Pressure over the chest, (3) Pressure on the head, (4) Palpitation, (5) Itching of the eyes, (6) Swollen glands, (7) Gasping for breath, (8) Sore throat, (9) Headache, (10) Congestion in the chest, (11) Difficulty in getting air through the lungs, (12) Belching, (13) Hiccups, (14) A bad sinus condition, (15) Pains in the stomach, (16) Weakness, (17) Dizziness, (18) Itching of the throat, (19) Swelling of the eyes, and (20) Swelling of the nose.

In the second visit, a new symptom, allergies to foods, was brought up. In addition, allergies to rain and water as well as possible psychological matters emphasized that this patient was not only possibly allergic but also suffered from a serious emotional disturbance. Thus, if the allergic concept is exchanged for the concept of mental illness we may view the symptomatology such as palpitation, pressure all over the body, sore throat, pains in the back, fever, weakness, dizziness, exhaustion, insomnia, photophobia, remaining in bed and in the house all day, difficulty in breathing, fear of bathing as well as other behavior problems, as more indicative of a serious mental illness. The patient's reading and contact with physicians enabled her to construct an allergic pattern which was more palatable to her than mental illness. The patient was referred to the Psychiatric Service of the Mount Sinai Hospital, New York City for diagnosis.

Course in Hospital.—The intake history and physical examination led to the following impressions: (1) Severe neurotic personality disorder, possibly schizophrenia, (2) Possible food or other allergies, and (3) No significant organic disease.

A complete set of intradermal skin tests to foods and inhalants was performed. The concentrations of pollen extracts used were as high as 20,000 phosphotungstic acid precipitable nitrogen units per cc. These were completely negative. In other words, there was no immunologic evidence whatsoever of an allergic status. According to the hospital records the patient revealed a well circumscribed delusional system with, however, a good grasp of reality outside of this system. The delusional system had to do with her father being in love with her, and with grandiose ideas of her own beauty and sexual attractiveness. On psychological tests, her Bellevue Scale IQ was 122, her Performance Scale IQ was 113, and her Full Scale IQ was 120. The patient was transferred to Hillside Hospital, New York, with a diagnosis of simple schizophrenia.

This patient is representative of what I believe to be a fairly large subdivision of Hoch's pseudoneurotic schizophrenia. In order for the physician who sees many allergic patients to satisfactorily utilize Hoch's concepts, and to attempt to establish a diagnosis of pseudoallergic schiz-

ophrenia as proposed in this paper, it is desirable to review very briefly Hoch's latest formulation. Hoch points out that this type of schizophrenia is essentially subtle with gross psychotic manifestations occurring only at times, and that the illness is characterized by the absence of gross psychotic symptoms like delusions, hallucinations and marked regressive phenomena. Hoch also points out that in the general classification of pseudoneurotic schizophrenia there is no single symptom. He divides the symptoms for diagnostic purposes into (a) impairment of emotional regulation, (b) impairment of thinking processes, and (c) impairment of action processes. Under Hoch's headings of a, b and c there are numerous practical subdivisions which may be used to classify symptomatology. In the case just presented there are many characteristics, such as underdevelopment of emotional regulation, impairment of empathy, lack of feeling tone, disorders of concept formation, unrelated ideas, stereotyped concepts, intellectualization of emotional responses, confusion of purpose, and distorted energy regulation with difficulty in regulating and systematizing activity, as well as autonomic dysfunction. In particular, the patient had seized upon autonomic dysfunction to account for the foregoing psychological distortions.

Case 2.—This patient was a single man, twenty-four years of age, who had been treated for seasonal and perennial hayfever for several years before he consulted me. In addition, his skin broke out with a neurodermatitis of the hands, neck, face and eyes, which incapacitated him and prevented him from working. The following comprise a partial list of things to which he felt he was allergic: All the common seasonal pollens, various flavors of ice cream, various vegetables, wool, silk, aftershaving lotion, tobacco smoke, drugs, talcum powder, dust, flowers, perfumes, carpets, soap, water, plastic sun glasses, and chocolate. Since somatic therapy failed, psychotherapy was begun. After twenty-five interviews practically complete elimination of all of the foregoing allergies occurred, even during the pollen season. The physical manifestations of allergy disappeared in a period of months. The following symptoms, however, appeared under different life stresses: immature emotional regulation, volatility of affect, poor regulation of aggression, intense need for ego support, a searching for reality contacts with low thresholds to frustration, and consistently structured unrealistic solutions. When magical gratification was not granted, allergic phenomena manifested themselves again. This patient could be fairly logical, thinking clearly with excellent concept formation in certain areas of coded conduct. There was, however, impairment of the thinking processes with an intense need to function according to a formula of what was needed on a symbolic level. These psychic difficulties were based on a fairly good reality structure which prevented the appearance of a frank psychosis. As far as energy regulation was concerned, there was dysregularity only when impairment of emotional regulation occurred. Autonomic dysfunction, especially, occurred with reference to those processes connected with skin, eye and nasal physiology, leading to violent exacerbations of allergic phenomena. This patient was classified as pseudoallergic schizophrenia with, however, less impairment of thinking processes as compared with Case 1. With little interruption of employment he has been successful in achieving some awareness of the way in which his undue symbolic processing has interfered with achieving the mature goals culturally demanded by his grasp of reality in certain situations.

Case 3.—This patient was a twenty-four-year-old man who lived with his father. He had no steady occupation. He had had asthma since he was sixteen, mostly in the winter. There were occasional summer colds. In the past year his asthma attacks had been milder but had necessitated treatment with epinephrine and aminophylin. He took care of an eleven-year-old brother at home and was worried about masturbation and sexual relationships. His mother had been institutionalized for mental illness.

I thought it odd that this young man was unemployed and was spending most of his time at home. I assumed at that time that he was one of the casualties of the allergic state; a young man with asthma who was chronically disabled and unable to function because of severe episodes. Intradermal tests were negative. Examination showed his skin and chest to be negative. His asthma was treated symptomatically with some relief. When he was under emotional stress, sodium amobarbital was effective. He responded well to observation and treatment for two years, with nothing unusual noted and his asthma fairly well controlled. One day I received a telephone call from his father telling me that his son had been hospitalized at Bellevue Hospital. It appears that he had become dissatisfied with my treatment and had visited another doctor for therapy for his allergies. He got into some type of altercation with this doctor and threatened him. The doctor called the police and the patient was hospitalized at Bellevue in the Psychiatric Ward. He was there for a brief period and then discharged. The report from the hospital read as follows: "Patient is a twenty-six-year-old male who has been suffering from bronchial asthma for several years without any prominent relief of his symptoms. He is a very flat person. His judgment was impaired and his insight almost nil. Final diagnosis—schizophrenia."

This patient was first seen by me more than ten years ago. At that time I did not understand the way in which an allergic pattern could act as screening smoke to a more serious mental process which in this case was schizophrenia. His chart revealed certain symptoms of which he complained; a sore spot in the middle of his lip, a feeling of something running loose, a running shaking sensation in certain spots, a jumpy feeling, pains all over, palpitation, weakness in walking, worry concerning his asthma, and a warm feeling in his chest. I believe that with my present knowledge of this complicated syndrome I would be better able to manage this patient.

Case 4.—This patient was a thirty-eight-year-old married woman, who, up to the time of her marriage had been "healthy, happy and contented." She taught ballroom dancing, loved music, and played the piano. She had been married for one year. She complained of hives, asthma, itching and cramps. She felt that her difficulties went back to a sigmoidoscopic examination during which she screamed with pain and had severe pains inside her abdomen, with loose bowels, bloody stools and cramps ever since. She blamed the following symptoms on this rectal examination: itching in the rectum, itching in the vagina, funny sensations in her body, hives all over her body, throat full of "beads," weak heart, difficulty in breathing and swallowing when alone, numbness in her rectum, feelings of vibrations in a car or bus which were severe enough to make her get up and leave and swelling of her vagina. She blames some of her symptoms on a woman doctor who did a vaginal examination and used a speculum. She said, "I am built small. There is a swelling there but I try having intercourse." Her husband stated, "Everything started six days after marriage." The patient kept emphasizing throughout her interview, "I got sick because of a doctor."

The patient had been treated by an allergist for her numerous allergic symptoms. However, it is quite obvious that she was unable to deal with marriage and blamed the doctor for all of her symptoms and all of her difficulties which occurred after

her marriage. She was unable to face the fact that her relationship with her husband was involved. This patient's lack of insight, and her inability to deal with her difficulties, except in a paranoid fashion, fits her into the category of pseudo-allergic schizophrenia.

TABLE I. SYMPTOMS OF PSEUDONEUROTIC SCHIZOPHRENIA*
(6 Cases)

Impairment of Emotional Regulation	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
1. Underdevelopment of emotional regulation.	+	+	+	+	+	+
2. Volatility and insufficient modulation of, or no modulation and absence of emotional response.		+	+		+	+
3. Inability to regulate aggression. Gross ambivalence.		+	+			
4. Desire for versus rejection of protection. Dependency craving and need for ego support.	+	+		+	+	+
5. Craving for reality contact versus repudiation of it.	+	+		+		
6. Impairment of empathy.	+	+	+	+	+	+
7. Great sensitivity. Ego referential; everything has meaning as related to the ego.	+	+	+			+
8. Impairment of self-assertion. Sense of inferiority and failure.	+	+	+		+	
9. Lack of feeling tone. Emulates behavior of others to achieve emotional feeling. Search for experience.	+	+	+	+	+	
10. Intolerence to tension. Low threshold to frustration. Striving for quick, magical gratification.	+	+		+		
Impairment of Thinking Processes						
1. Paralogic thinking. Catathymic thinking. Categorical impairment.	+	+		+		+
2. Disorders of concept formation and of ability to think abstractly. Concretization.	+		+	+		
3. Loosening of associations. Liberal use of symbolic connections, and misuse of logic.	+	+		+		
4. Feelings of unreality, depresonalization, being hazy, doped, dazed. Fantasy-reality border is shaky.	+					
5. Complex-bound associations.			+			
6. Pseudophilosophizing with confused, esoteric debates about love-hate, life-death, etcetera.					+	+
7. Inflexible, stereotyped concepts about self. Universal concepts on basis of limited experiences.	+			+	+	+
8. Inclination to handle situations with intellect as substitute for emotional response.		+		+	+	
9. Dominating fantasy life which cannot be turned off at will, or repudiation of fantasy life.	+	+				
10. Confusion of aims and purposes, of means and goals.	+		+	+	+	
11. Urge to function according to formulas.	+					+
Impairment of Action Processes						
1. Symptoms						
(a) Pan-anxiety.	+	+		+		
(b) Pan-neurosis.						
(c) Pan-sexuality.						
2. Energy regulation						
(a) Dysregulation of energy output.	+		+	+		
(b) Difficulty in initiating, sustaining, and/or stopping activity.	+		+	+	+	
3. Autonomic dysfunction.						
(a) Low threshold to organ or system dysfunction in association with anxiety.		+	+	+	+	
(b) Lack of vegetative homeostasis						

*Modified from Hoch.
Symptoms tabulated according to impairment of emotional, thinking, and action processes.
One symptom is not pathognomonic. Several must be present.

Case 5.—A thirty-year-old woman with persistent eczema was treated from both an allergic and psychiatric point of view for over one year. Her allergies were mainly connected with generalized neurodermatitis of the skin. Social adjustment was fair and outwardly there was a good relationship with a limited number of people. However, there was such a serious impairment of emotional regulation, energy regulation and autonomic dissociation that I am inclined to consider the basic process as schizophrenic because of the large number of symptoms enumerated in Table I.

Case 6.—This patient was a married woman of forty who had several children. She had been married for fifteen years and had been frigid with her husband during this entire period. She also openly resented sexual approaches on his part. For several years before coming for treatment she had gradually become allergic. Food allergies increased in number and intensity so that her physical complaints of nausea, diarrhea, abdominal cramps, mysterious upsets, blind headaches and vomiting spells were successfully controlled by elimination of these foods. When she was first tested to foods she could not tolerate all meats, eggs, fowl, fish, nuts, beans, peas, cauliflower, peaches, pineapple, cottonseed oil, coffee, pears, sour milk, and tomatoes, among other foods. Gastrointestinal series including a barium enema were negative. Intradermal skin tests revealed nothing of significance. A food diary gave no definitive information. She first thought that her symptoms were due to allergy when a doctor attempting to explain her symptoms to her said, "Have you thought of allergy?" Temporary relief was obtained from nostrums which were unconnected with allergic problems.

The patient was treated psychiatrically and in the course of several months she became able to tolerate foods to which she thought she was allergic. She gained weight, and was finally discharged as very much improved, with *no* allergies to foods. Her psychodynamic structure is indicated in Table I and she is considered to fit into this category of pseudoallergic schizophrenia on the basis of her improvement under psychotherapy and her psychological attitudes.

DISCUSSION

Table I summarizes the way in which we have viewed our allergic cases against the background of Hoch's criteria. Table I is essentially that published by Hoch but is somewhat abbreviated.

Table I is very useful for evaluating the psychological status of the allergic patient who does not respond, or who responds too rapidly to therapy. The schizoid personality often becomes rapidly (magically) cured when a new medication is used or when a new physician is brought into the therapeutic situation. Unless the rapid recovery is consistent with the pharmacologic action of the medication employed, one must look for psychological forces as being an important part of the pattern of response. Of course, supportive and other psychological measures may play an important role in the patient who does not have a schizoid personality structure. However, using Hoch's criteria, I have found with experience that a suitable diagnosis of the personality structure is of the utmost importance in the achievement of realistic therapeutic goals.

The fact that the patient fits in with the diagnosis of pseudoallergic schizophrenia should not prevent the physician from treating in the usual way the asthma, eczema, hives and other symptoms present. These patients may respond well to epinephrine, ephedrine and steroid therapy in very much the same way that patients with more normal personalities respond. More often they do not respond to ordinary hyposensitization with allergens. None of the six patients diagnosed here as pseudoallergic schizophrenics responded to hyposensitization except temporarily. In view of the essentially slow rate of deterioration of these patients, psychodynamically, they provide the physician with an opportunity to treat the

latent syndrome of schizophrenia without the immediate danger of acute unmanageable psychotic episodes. For this reason, I believe that the physician who is willing to treat these patients from a psychologic point of view more often than not may find his efforts rewarded with a certain degree of success.[3]

On the other hand, the physician should be cautious before removing the allergic symptomatology if this is the bulwark of defense against the eruption of schizoid drives. Certainly, the patient should not be abruptly told that he must face the fact that he is a psychological problem. Rather, the opposite is true. The patient should be slowly and carefully brought into touch with the real nature of his symptoms in terms of the allergic complaints. As realistic appraisal of the allergic symptoms becomes understood, the presence of conflicts in the patient may be gradually brought into focus with the physician always prepared to deal with a more severe personality disorder.

The question arises as to whether it is worthwhile to permit the patient to maintain the fictitious allergy in order to preserve, in hidden recesses of his personality, the schizophrenic patterns. I believe that the data in this paper cannot answer this question; but as systematic data are accumulated and studies made over periods of years, more valid conclusions may be drawn. In cases of asthma where the intensity of the asthma is an expression of a psychiatric process, the great danger is that it may lead to the death of the patient. In these cases, psychotherapy is certainly always indicated. When the eczema completely disables, psychotherapy cannot be avoided, even in the presence of calculated risks.[4]

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CHRONIC BRONCHITIS

Chronic bronchitis refers to the condition of those patients suffering from chronic or recurrent cough and expectoration and usually effort dyspnoea, in whom these symptoms are not caused by disease of the lungs, by localized disease of the bronchi, trachea or upper respiratory tract, or by primary cardiovascular disease.—J. G. SCADDING: Quart. J. Med., 21:460, 1952.

SULFONAMIDE THERAPY IN THE PREVENTION OF ASTHMA ASSOCIATED WITH INFECTION

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INFECTION frequently provokes or prolongs attacks of asthma in certain patients despite conscientious hyposensitization, elimination of allergens, removal of foci of infection, and vaccine therapy. Many of these patients are prone to repeated respiratory infections and may develop status asthmaticus, bronchiectasis, emphysema or other chronic lung diseases. In children these same infections may cause retardation of growth. The antibiotics have been of great value for such patients, but in those subject to repeated or prolonged attacks of asthma because of frequent respiratory infections, large doses of the antibiotics must often be used. Even though the antibiotic treatment is effective, the patient has already suffered physical and/or economic loss. It therefore seemed logical that the prevention of asthma associated with infection would be of decided advantage in selected patients.

The prevention of infectious diseases, particularly of coccal origin, first achieved measurable success with the discovery of the sulfonamide drugs. During World War II, case reports involving over 500,000 service men,[1-3] attested to the efficacy and safety of the sulfonamide drugs (sulfadiazine being used almost exclusively) in the prevention of streptococcal, pneumococcal and meningococcal infections, as well as causing a definite reduction in lobar pneumonia, atypical pneumonia, other respiratory diseases, and rheumatic fever. The incidence of toxic reactions was small in all these studies. Mild transient skin eruptions developed in no more than 0.3 to 0.6 per cent of the patients, while serious reactions such as exfoliative dermatitis and agranulocytosis were exceedingly rare. Many other studies on a much more prolonged basis affirm the excellent results and low toxicity of the sulfonamide drugs in the prevention of bacterial infections, including rheumatic fever.[4-10] Thomas[11] advocated the continued use of sulfonamide drugs for periods of five years or more in the prevention of rheumatic fever and observed a marked decrease in the incidence of most bacterial infections. Purdy,[12] sixteen years later affirmed the uniformly good results in the prevention of rheumatic fever when treatment was carried out for three to five years or longer. She preferred the sulfonamide drugs to penicillin which was reserved for emergencies or sulfonamide-sensitive patients.

With this extensive clinical background the use of the sulfonamide drugs to prevent asthma associated with infection was undertaken about ten years ago.[13]

At that time, twenty patients in whom the avoidance of allergens,

hyposensitization, removal of foci of infection, rhinologic, bronchoscopic, drug and vaccine therapy had failed, were selected for prophylactic therapy with sulfonamide drugs. Although antibiotics often helped these patients, they had to be given frequently because of repeated respiratory infections. These patients were given 0.5 to 1.0 gm of a sulfadiazine-sulfamerazine mixture daily for seven to nine months. The results were unusually favorable and no adverse reactions occurred.

Since that time, the same procedure has been followed in seventy-one additional patients over the past ten years with the substitution of a triple or quadruple sulfonamide for the double preparation. Other favorable reports concerning the use of antibiotic and sulfonamide drugs in the prevention of asthma associated with infection have appeared in the interim.[14-19] We had considered using penicillin prophylactically (it was the only available antibiotic at that time) but the clinical success of the sulfonamide drugs in hundreds of thousands of patients in preventing various respiratory infections of bacterial origin, as mentioned previously, with minimal toxic reactions, influenced us to use the sulfonamides. As time has borne out, the newer antibiotics have not been free of side effects and serious complications, in addition to being considerably more expensive.

METHOD

This type of therapy was applied to those patients who suffered from perennial asthma or from repeated attacks of asthma from early fall until the summer, year after year. These attacks were thought due to bacterial infection or to infection (particularly upper respiratory tract infection) superimposed upon other agents producing asthma. This included a large number of allergic individuals in whom, because of infection, the asthmatic symptoms continued even when the atopic factors were eliminated or treated.

The selection of patients in whom infection was felt to be an important factor was made chiefly on a clinical basis, since laboratory tests are frequently not conclusive in differentiating infectious from noninfectious asthma. The history is most important, but physical examination and other studies may be significant in establishing the presence of infection.

The following criteria were used to distinguish the infectious from the noninfectious asthmatic patient, although exceptions may occur.

History.—

1. A history of asthma uncontrolled throughout most of the year with relief in the summer months (although in some, asthma may be perennial).
2. A history of asthma controlled until a respiratory infection occurred, or a history of many colds followed by asthma, although other allergic conditions had been eliminated or treated.

3. A history of purulent nasal or bronchial secretions, with difficulty in controlling attacks of asthma.

4. A history of relief from anti-bacterial measures, other treatment failing.

5. A history of relief when the patient was removed from adverse weather changes, as in warmer climates where respiratory infections were minimal.

The presence of several of these factors in one patient provided stronger evidence than any one alone that the asthma was associated with infection.

Physical Examination.—

1. Presence of purulent nasal, post-nasal or bronchial secretions.

2. Presence of enlarged cervical glands and/or inflamed pharyngeal tissue or other evidences of infection.

3. Increased pulse rates and temperature elevation obviously suggest infection, but asthma associated with infection was frequently present with normal pulse rates and normal temperature readings.

Laboratory.—Blood counts, sedimentation rates and x-ray examinations were significant in some instances, but often did not correlate with the historical findings. In many instances, the history was considered as most important in the differential diagnosis of infectious asthma.

Controls.—No control patients were used in this study for several reasons.

1. There were not enough patients of similar type presenting themselves at the same time and subject to similar economic, environmental, or atopic factors to serve as control patients.

2. The evaluation of control patients in such a varying disease is most difficult. However, those patients who were followed for several years served as their own controls. For example, those previously afflicted year after year were remarkably free of severe attacks of asthma on prophylactic sulfonamide therapy. The following season without prophylaxis, asthma recurred. Resumption of sulfonamides the year following, again resulted in favorable effects. Even during one season, when a patient may have become careless in taking the sulfonamide drugs with resultant asthma after a respiratory infection, the resumption of sulfonamide therapy prophylactically again kept the patient out of difficulty. This occurred in nine patients.

Dosage.—One gm daily of a mixture of three or four sulfonamides was administered from September to June, four patients being kept on perennial therapy when attacks occurred in the summer following respira-

tory infections. Smaller doses were given in accordance with age and to those with impaired renal function. The triple mixture consisted of equal parts of sulfadiazine, sulfamerazine and sulfamethazine, while the quadruple mixture also contained sulfacetamide. The sulfonamide mixtures were administered to patients ranging from three to eighty-eight years of age.

RESULTS

The seventy-one patients were divided, according to therapeutic response, into four groups as shown in the accompanying table.

EFFECT OF SULFONAMIDES IN PREVENTING ASTHMA ASSOCIATED WITH INFECTION IN SEVENTY-ONE PATIENTS

Effect	Excellent Results: No Loss of Time From Work or School Due to Asthma	Good Results: Occasional Attacks of Mild Asthma Easily Controlled	Discontinued Therapy Because of Side Effects (Nausea)	No Benefit
Number of patients	42	18	2	9

Further Observations.—Nineteen patients have been on this therapy for four years and two patients for eight and nine years respectively without any ill effects. Seven patients had relief from asthma on using the sulfonamides even when anti-allergic therapy was irregular. Eight have followed this procedure for a year or more and then stopped with good results even when the sulfonamides were not resumed the following year.

We do not know how long this therapy should be continued, just as we do not know how long we must hyposensitize for pollens and dust.

Of the treated patients who developed asthma following an infection, control of the attack was quickly obtained with antibiotic agents. With the continued use of sulfonamides, further attacks rarely occured.

Reactions.—There were no serious reactions or complications in the seventy-one patients. Prophylactic therapy with the sulfonamide mixtures never had to be interrupted because of renal damage, bone marrow depression or skin manifestations. Only two patients of this entire group discontinued therapy and that was because of nausea.

CASE REPORTS

Case 1. M.G., a three-year-old child, who since the age of six months had frequently recurring attacks of asthma and bronchitis associated with high fever throughout the fall, winter and spring, despite weekly injections of dust and vaccine. Penicillin and other antibiotics were required. The child was usually well through the summer. The family history revealed that the mother had grass and ragweed pollenosis and the grandfather was an asthmatic.

Daily doses of 0.5 gm of triple sulfonamides were started in January, 1954, after she had four recurrences of asthma and bronchitis with fever, each lasting

from one to two weeks. Injections of house dust and vaccine were continued. No attacks of asthma, bronchitis or fever occurred through the remainder of the winter and spring, although she had several upper respiratory infections which now appeared trivial. The child gained five pounds between January and June.

In the fall of 1955, prophylaxis with sulfonamide drugs was not instituted but injections of house dust and vaccine were continued. Attacks of asthma associated with bronchitis recurred frequently and were treated with the antibiotic drugs. These attacks continued for several months, the child losing weight and becoming anemic. In February, 1956, she resumed therapy with sulfonamide drugs and had no further attacks of asthma.

Case 2. A.C., a forty-five-year-old woman, had perennial asthma for six years, although prior to the past two years the attacks had not been present during the summer. She had been hospitalized several times because of severe asthma and lost so many days from work at various times that she was on the verge of losing her job. She had been skin tested and treated without relief. She continued to have repeated respiratory infections. In the past year she developed an allergy to penicillin and had to be transferred from her department at Wyeth Laboratories where she was in contact with the drug. She had no previous history of allergy. Her father had hay fever.

In late September, 1955, after many asthmatic attacks, 1.0 gm of triple sulfonamide drugs daily was instituted. By early October she had improved and the improvement continued steadily. She was able to sleep throughout the night for the first time in months. No further severe attacks of asthma occurred. She lost no time from work, and now was able to put in many hours of overtime. The sulfonamide drugs were stopped June 15, and the patient continued in good health until July 24, when she developed an upper respiratory infection after being exposed to members of the family who had colds. This was followed by a cough, expectoration of yellow mucus and asthma. Sulfonamide drugs were resumed on August 14. Improvement soon followed and the patient has remained well, while continuing the sulfonamide drugs prophylactically. The patient is still under this treatment and has remained symptom-free.

Case 3. W.P.M. first came under my observation sixteen years ago at the age of seventy-two. He had a history of asthma for over thirty years during the ragweed pollen season. With hyposensitization the hay fever improved considerably, but asthmatic attacks become more prevalent during the late fall, winter and spring. The attacks became increasingly severe and with each respiratory infection he was ill with severe asthma for periods of from three to six weeks. Injections of house dust and catarrhal vaccine were administered in addition to ragweed pollen extract, but severe attacks of asthma followed upper respiratory infections. Pneumonia occurred once yearly from 1944 to 1948. By this time his hay fever no longer annoyed him and he did not have attacks of asthma during the pollen season. His asthma now appeared to be due to infection alone. Sulfonamide drugs, 0.5 gm daily, were started in September, 1948, and for the first time in five years he was free of pneumonia and asthma. An upper respiratory infection did not result in asthma. In 1949, the same procedure was followed with similar results. This was repeated yearly with the same favorable effects. In 1952, a cough resulted from paralysis of a vocal cord due to a cerebrovascular accident, but no asthma occurred. In 1955, he developed urinary difficulty due to an enlarged prostate gland. An operation was not feasible because of a large scrotal hernia that made the procedure almost impossible technically. The prostate was found to be malignant and an indwelling catheter was used until his death

in 1957. He was bedridden for fourteen months, during which time he was on continuous sulfonamide therapy. No asthmatic symptoms occurred during those months.

This patient, who died at age eighty-eight, had been on sulfonamides for over eight years with excellent results and no adverse reactions.

Case 4. L.B., a forty-five-year-old man, first developed asthma following pneumonia eleven years ago. His attacks became progressively worse with short intervals of relief during the summer and once on a vacation in Florida. He also gave a history of many upper respiratory infections. The only positive skin tests were moderate reactions to dust and mixed catarrhal vaccine. Previous methods of treatment had failed. He was given penicillin with marked improvement, only to relapse when the penicillin was discontinued. He was unable to work in the winter and spring of 1950 and 1951 because of asthma. Injections of dust and vaccine were administered without controlling the symptoms. Penicillin given parenterally at the time of an attack relieved him quickly. A triple sulfonamide mixture was started in September, 1953, and continued until June, 1954. He was well during this time but did not resume treatment until June, 1955, although his asthma returned in December 1954. This was controlled with penicillin and the sulfonamide drugs were reinstituted, at his request, in September, 1955. He has continued to receive injections of dust and vaccine in addition to the sulfonamide drugs and has been free of severe attacks with no loss of time from work from September, 1955, until the present.

Case 5. C.A., a twenty-two-year-old woman, developed asthma at the age of seven, her attacks developing into status asthmaticus, particularly during fall, winter or spring. She had been hospitalized many times because of the severity of her asthma, and had been found sensitive to cat hair, house dust, feathers and goat hair. There was a family history of allergies. Removal of positive factors and dust hyposensitization did not prevent severe attacks during the fall, winter or spring. At the age of fourteen, she was sent to Arizona and there was free from attacks from October to May. When she returned home she was well until October when she again developed severe asthma. After her symptoms were controlled with penicillin and bronchodilator drugs, she was given the sulfonamide drugs. She was free of asthma during the winter and spring, although a respiratory infection occurred in March. Sulfonamide drugs were again started after the summer and she had an excellent response for the remainder of that year (1951) and in 1952.

This young woman has not been under allergic management nor has she had sulfonamides or other drugs since 1953. She was free of symptoms until August 1956, when for the first time she developed hay fever. However, she has had no recurrences of asthma.

DISCUSSION

Research and clinical experience have shown that the majority of respiratory infections are sensitive to the sulfonamides and that the triple or quadruple mixtures produce an additive bacteriostatic effect, while the combined drugs retain their independent solubilities in the urinary tract. With these sulfonamide preparations there is a low incidence of sensitization and of adverse effects on the kidney.[19,20] Prophylactically they provide an effective answer to the problems of hypersensitivity, drug resistance and superimposed infections which have occurred with antibiotic

therapy and which indicate the desirability of reserving these potent agents for infections resistant to the sulfonamides.

With the discovery of better antimicrobial agents of low toxicity, low antigenicity, and a minimum of side effects, this problem will be more adequately handled. We are of the opinion that until then the sulfonamide mixtures meet these requirements as well as and with no greater danger than the antibiotics now available for the prophylaxis of asthma associated with infection. These other antibacterial agents can be held in reserve for emergencies.

SUMMARY AND CONCLUSIONS

1. Triple or quadruple sulfonamides were used to prevent asthma associated with infection in patients whose conditions were not controlled by allergic or other measures.

2. Seventy-one patients ranging from three to eighty-eight years of age were given through most of the year, in doses ranging from 0.5 gm to 1.0 gm daily, a triple or quadruple sulfonamide drug as prophylaxis against asthma associated with infection. The usual antiallergic procedures were continued in most of these cases.

3. Forty-two patients had excellent results as evidenced by no loss of time from work or school due to asthma. Eighteen patients had good results, the occasional attacks of asthma being milder and more easily controlled. Nine patients had no benefit. Two patients stopped therapy because of nausea.

4. There were no untoward reactions excepting for two instances of nausea.

5. We can conclude that the prophylactic administration of the sulfonamide drugs in conjunction with allergic and medical management is of value in asthma associated with infection. The triple or quadruple mixtures of sulfonamides are as free from reactions as other antibacterial agents and permit the use of the latter agents for other intervening or superimposed infections.

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SCIENCE AND SKEPTICISM

Let me be clear. Science is not skepticism. It is not the practice of science to look for things to doubt. It was not by a deliberate attempt of skepticism that physicists were led to doubt the absolute nature of simultaneity, or to recognize that the ideas of strict causality embodied in classical physics could not be applied in the domain of atomic phenomena. There is probably no group of men who take more for granted in their daily work than the scientists. Common sense and all that flows from it are their principal basis for what they do in the laboratory and for what they make of it on paper. But for scientists it is not only honorable to doubt; it is mandatory to do that when there appears to be evidence in support of the doubt. In place of authority in science, we have and we need to have only the consensus of informed opinion, only the guide of example. No scientist needs to order his colleagues to use a new technique of experiment or to enter a new field of discovery. If he has done this, it will be an invitation to his fellows to follow.—J. ROBERT OPPENHEIMER, *The Open Mind*, Simon and Schuster, 1955.

THE EFFECT OF MIGRATION TO MIAMI, FLORIDA ON ALLERGIC RESPIRATORY DISEASE

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BETWEEN 1950 and 1956 the population of Florida increased by about one million people. This represented a 40 per cent increase in total population, the highest percentage increase of all the states. In 1956, Florida had the largest population gain of all the states as a result of migration alone. In addition, more than four million tourists visit the greater Miami area each year.

While most of these people came to enjoy the pleasant climate, many sought relief from respiratory disease. Because of this growing tendency to seek relief by migration, a survey to determine the results was thought to be of value.

PREVIOUS STUDIES

Metzger[3] in 1939 drew the first discouraging picture of the effect of migration in the treatment of allergic respiratory disease. He stated that, in Tampa, Florida, in a practice confined exclusively for years to the treatment of the allergic diseases, there had come under his observation too small a number of patients who had found relief through climatic change to warrant this form of treatment. He did, however, concede that most persons sensitized to ragweed are free from symptoms in Florida.

In 1951, Zivitz[6] studied 150 known allergic individuals who came to the Miami area for an extended period of time. He concluded that 17.7 per cent obtained prolonged relief, 37.1 per cent had temporary benefit, and 45.2 per cent were not improved. He felt that there was also a small group of patients of undetermined number who obtained complete and prolonged relief by residence in Miami, but since they sought no medical aid, were statistically unknown. He suggested that northern allergists could contribute to the study of this group.

In 1954, Marks[2] reported on Florida climate as an influencing factor in childhood allergy. He felt, as a result of his personal experience and through tabulation of a questionnaire sent to Florida pediatricians and allergists, that though some migrant patients are improved, they are few in comparison with those who are either not improved or who are made worse.

This generally discouraging consensus summarizes the published expression of Florida practitioners. In contrast, in 1948 Schutzbank[5] reported on 100 patients who migrated to Tucson, Arizona, and were observed for

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one year or more. He found that 76 per cent were benefited by climatotherapy and that 24 per cent were not appreciably helped.

METHODS

The information given in previous studies was obtained from selected groups of allergic individuals who had sought out allergists in their new environments. One does not expect to find healthy people in a physician's office. A better analysis might be had by interviewing people at random.

Accordingly, people who were attending the surgical, general medical, orthopedic, dermatologic, pediatric, obstetric, neurologic, endocrine, and cardiac clinics at the Jackson Memorial Hospital were interviewed concerning their past experiences with asthma, allergic rhinitis, and hay fever. These people were questioned at random and the first fifty who gave a past or present history of one of the above diseases and who also had resided for at lease one year in another state and for at least one year in Miami were included in the so-called *random* group.

In addition, 100 patients attending the Allergy Clinic at Jackson Memorial Hospital were interviewed. These patients, too, had resided in some other state for at least one year and had resided in Miami for at least one year. They were selected at random from the whole clinic population and were termed the *allergic patients* group.

All of the people interviewed were asked if they had experienced asthma, allergic rhinitis, or hay fever while they had lived in another state. Those who had were then asked whether they had improved, remained the same, or became worse since they had moved to Miami.

It was believed that the terms *asthma, allergic rhinitis,* and *hay fever* would be as well understood by lay people as by physicians, and the experience gained in making this survey confirmed such a belief.

RESULTS

It was necessary to interview at random almost 1000 people to discover thirty-nine who had a past history of allergic respiratory disease. Since the population of the greater Miami area is about 700,000, this sample group of thirty-nine would represent a total population group of approximately 28,000 people who had suffered from allergic respiratory disease in some other state and had come to Miami.

Table I shows the symptoms that patients in both groups complained of before they came to Miami. Thirty-four per cent of the allergy clinic group and 22 per cent of the random group had been symptom free. In the allergy clinic group, forty-four people had suffered from asthma, forty-three from allergic rhinitis, and twelve from hay fever before they had moved to Miami. In the random group, twenty-six people had experienced asthma, fourteen allergic rhinitis, and nine had had hay fever before they had moved to Miami.

The effect of migration on the manifestations of each of the three diseases is shown in Table II. While only 37 per cent of the asthmatic patients in the allergy clinic group improved, 77 per cent of the asthmatics

TABLE I. SYMPTOMS PRESENT BEFORE MIGRATION TO MIAMI

Symptoms Before Coming to Miami	Allergic Patients	Random Group
Asthma	17	18
Perennial rhinitis	14	4
Hay fever	5	7
Asthma and perennial rhinitis	23	8
Asthma and hay fever	1	0
Perennial rhinitis and hay fever	3	2
Asthma, perennial rhinitis and hay fever	3	0
No symptoms	34	11
Total	100	50

in the random group improved. Also, while only 26 per cent of the allergy clinic patients with allergic rhinitis were improved, 86 per cent of those with allergic rhinitis in the random group were improved. Of the twenty-one persons in both groups who had had hay fever, only one was not improved in Miami.

TABLE II. EFFECT OF MIGRATION TO MIAMI ON PRE-EXISTING ALLERGIC SYMPTOMS

Symptoms	Number	Improved	No Change	Worse	Not Benefited Per Cent
Allergic group:					
Asthma	44	16 (37%)	11	17	63
Perennial rhinitis	43	11 (26%)	21	11	74
Hay fever	12	11 (92%)	1	0	8
Random group:					
Asthma	26	20 (77%)	4	2	23
Perennial rhinitis	14	12 (86%)	1	1	14
Hay fever	9	9 (100%)	0	0	0

A number of people in both groups had experienced more than one manifestation of allergy. Obviously if one manifestation was relieved, but another became worse, the individual would not have been helped much. Also, a number of people had completely lost one manifestation of allergy, only to develop a totally new one. Accordingly, each of these people was asked if migration had helped his allergies as a whole. Table III reflects the replies to this question. In the allergy clinic group only 29 per cent experienced over-all improvement, but in the random group 80 per cent were thus improved.

In Table IV is shown the fate of the thirty-four people in the allergy clinic group and the eleven people in the random group who were symptom-free before they came to Miami. Alone or in combinations, thirty developed asthma, twenty-four developed allergic rhinitis, but only two developed hay fever.

A number of people had one manifestation of disease before moving and

developed a substitute or additional symptom after moving. Table V shows that fifteen developed asthma, seven developed allergic rhinitis, and only one developed hay fever.

TABLE III. EFFECT OF MIGRATION TO MIAMI ON ALLERGIC PATIENTS AS INDIVIDUALS

Number Patients	Improved	No Change	Worse	Not Benefited Per Cent
Allergic group: 66	19 (29%)	12	35	71
Random group: 39	31 (80%)	5	3	20

Thus, of the 150 people interviewed, forty-five reported the onset of asthma, and thirty-one reported the onset of allergic rhinitis in Miami. Only three reported initial symptoms of hay fever in Miami. However, while more than 50 per cent of the allergy clinic group had the onset of a new symptom in Miami, less than 30 per cent of the random group had been so afflicted.

TABLE IV. SYMPTOMS DEVELOPED IN MIAMI BY PREVIOUSLY ASYMPTOMATIC PERSONS

Symptoms Developed In Previously Well People	Allergic Group	Random Group
Asthma	15	4
Perennial rhinitis	9	5
Hay fever	1	0
Asthma and perennial rhinitis	9	1
Asthma and hay fever	0	1
Total	34	11

Investigation of the twelve patients in the allergy clinic group who reported relief of *hay fever* revealed that five developed asthma which replaced the hay fever; one developed allergic rhinitis; in two, a co-existing asthma became worse; in one, a co-existing allergic rhinitis became worse; all occurred after migration.

TABLE V. ADDITIONAL SYMPTOMS DEVELOPED IN MIAMI BY PERSONS WHO HAD PRE-EXISTING SYMPTOMS

New Symptoms Developed After Moving to Miami	Allergic Group	Random Group
Asthma	14	1
Perennial rhinitis	6	1
Hay fever	0	1
Total	20	3

In contrast, in the random group, investigation of the nine patients reporting relief of *hay fever* revealed that only one developed asthma which replaced the hay fever.

The factors of sex, race, and previous place of residence seemed to have no bearing on whether or not people improved. However, the average age of the patients who improved was forty-seven years, and the average age of the people who did not improve or who developed initial symptoms in Miami was forty-one years. The average length of residence in Miami for the people who improved was nine years, and the average length of residence for those who did not improve or who developed initial symptoms in Miami was twelve years.

DISCUSSION

The striking finding of this survey was the marked difference in the result, depending on the group from which the sample is drawn. As Marks pointed out, the feeling among Florida physicians is that migration to Florida does not benefit the patient with allergic respiratory disease. However, I feel that the experiences of these physicians, as well as the experiences of Metzger and Zivitz, have been with a select group of people similar to the people in this *allergy clinic group*.

I feel that the study of a selection of people at random has indicated that a substantial number of people *are* relieved of their allergic symptoms by migration to Florida alone.

Whether or not the same relief could have been obtained by migration at home to around the corner is the point at issue. It has been determined that in a population of 700,000, about 28,000 arrived with some sort of respiratory allergy and did not seek further medical care. Of this number, 22,500 improved without further treatment. These numbers need comparison with studies done on migration to other communities and migration within communities.

This report attempts to describe only *what* happens to allergic people who move to Miami. Unfortunately, it is not possible to explain *why* it happens. As Zivitz has pointed out, further study of this problem involves co-operation between allergists of Miami and of other states. It also involves arriving at a better understanding of the etiologic factors in southern Florida. This is a problem which is being pursued vigorously at the present time.

We have, however, happily demonstrated that almost everyone who suffers from seasonal hay fever will improve in Miami. Almost all of the people who developed distressing symptoms to replace the hay fever were in the select *allergy clinic* group. In the random population, people recovered from hay fever and stayed well.

The absence of hay-fever patients in our large allergy clinic at the Jackson Memorial Hospital confirms our belief that hay fever is a rare condition in Miami. With almost 4000 patient visits per year we see only two or three people who experience anything resembling seasonal hay fever.

Unfortunately, it cannot be claimed that residence in Florida is good prophylaxis. A substantial number of people in both groups noted the onset

of their symptoms in Miami. However, very few experienced the onset of hay fever.

SUMMARY

A study of a group selected at random from the general population of the Miami, Florida, area indicates that a substantial number of people with allergic respiratory disease will improve as a result of migration to Miami alone.

A similar study of a group selected from among patients attending the Allergy Clinic at Jackson Memorial Hospital indicated that a substantial number of patients with allergic respiratory disease will not improve as a result of migration alone. It is suggested that because this is a selected group of patients the results do not reflect the results in the population as a whole as do the results of the study of a randomly-selected group. Since the results of the study of this group correlate with the previously published expressions of medical opinion, it is suggested that previous reports were based on observations of selected rather than random groups.

Analysis of these groups indicates that hay fever is a rare manifestation of allergy in Miami.

The results indicate that it is possible to develop initial symptoms of asthma or allergic rhinitis in Miami.

Sex, race, and previous place of residence do not seem to play a part in improvement. However, age and length of residence in Miami may be of slight importance.

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A LONG-ACTING TRIPLE ANTIHISTAMINE

Preliminary Report

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THE SUBJECT of this preliminary report is a long-acting triple antihistamine, designated by the trademark, Tridecamine.* The dose of each of the three antihistamines in the tablet is one-third that usually administered over a twelve-hour period. Laboratory studies show that the medication is released continuously from the special base for a period of eight to eleven hours.[2] Duration of action has been confirmed in human subjects by measuring the size of the wheal produced by an intradermal injection of 0.1 cc of a 1:10,000 dilution of histamine diphosphate every two hours.[2] Such studies indicate that histamine is antagonized for as long as fourteen hours following administration of a single dose of Tridecamine.

The individual antihistamines were selected partly because they are established agents in the symptomatic treatment of allergic diseases and partly because each represents one of the three major chemical groups of antihistamines.[1] This formulation was chosen so that therapeutic effects would be additive and side effects would be minimized. Moreover, the gradual release of medication might reduce further the incidence or severity of side effects, as it does when the same base is used for release of large amounts of nicotinic acid.[3] Specifically, the three antihistamines are doxylamine succinate, pheniramine maleate, and pyrilamine maleate. In each case the tablet contains 20 mg of the therapeutic agent.

CLINICAL TRIALS

During a twelve-month period from January, 1958, to January, 1959, Tridecamine was given to 284 patients seen in private practice. They ranged in age from fourteen to seventy-two years with the majority being in the twenty to forty years of age group. The indications for use in these 284 patients were the following:

Seasonal hay fever	172
Seasonal hay fever and asthma	37
Urticaria	40
Angio-edema	6
Perennial allergic rhinitis	22
Upper respiratory infection	7

The recommended dosage in all instances, regardless of age or clinical symptoms, was one tablet every twelve hours. The duration of therapy

*Tridecamine is the trademark of the Wm. S. Merrell Company, Cincinnati 15, Ohio, for a combination tablet containing 20 mg each of doxylamine succinate, pheniramine maleate and pyrilamine maleate.

with Tridecamine varied from a few days in patients with acute urticaria to several weeks in those with perennial allergic rhinitis. With few exceptions, Tridecamine was found to possess very adequate antihistaminic action, both in regard to immediate symptomatic response and sustained release effect. This preparation produced results equal to or superior to those obtained with other antihistaminic agents. This comparative estimate is based on the statements and the clinical courses of the patients in this study.

Seasonal Hay Fever.—One hundred seventy-two patients with symptoms due to grass, ragweed or mold sensitivity were given Tridecamine. Of the total number of patients in this classification, 114 were treated specifically with pollen, mold extracts, or both. The remaining fifty-eight patients were seen with the presence of seasonal symptoms or had preferred not to receive specific therapy. This division into treated and untreated groups was not on the basis of severity of symptoms. Good, satisfactory relief and comfort were experienced by all 172 patients. No attempt was made to grade the degree of relief since no true clinical measure was available. The patient's expression of comfort was accepted. There was a much quicker and more distressing return of symptoms with no medication in the patients who had received Tridecamine only as compared with those who had been given both Tridecamine and specific treatment. All patients were informed that the oral tablet was an adjunct to, rather than a substitute for complete adequate therapy. No recognized "side effects" were reported in this group. The pollen season in 1958 was "average" for the Midwest.

Seasonal Hay Fever and Asthma.—Thirty-seven patients with symptoms of seasonal hay fever and associated asthma due to grass, ragweed or mold sensitivity were treated with Tridecamine. Thirty-one patients also received specific pollen or mold therapy, and six patients, a bronchodilating agent. Nasal and eye symptoms were satisfactorily relieved but bronchial complaints were affected to an extremely slight degree if at all by the drug. Bronchodilatation was accomplished with oral or nebulized preparations. No side effects were reported or noted in this group.

Urticaria.—The over-all response to this form of antihistaminic therapy was excellent in forty patients. Tridecamine was *not* used in urticarial reactions induced by penicillin or serum, because of failure of this type lesion to respond to other antihistaminic preparations. Tridecamine was discontinued in four patients of this group because of drowsiness, and in one, because of nausea. This latter patient was unable to use other antihistamines, but the four patients who became drowsy were comfortable while taking other antihistaminic drugs. Lower dosage would probably not have produced these side effects.

Angio-edema.—The swelling was not influenced by the use of Tridecamine in six patients. No side effects were noted in this group.

Perennial Allergic Rhinitis.—Twenty-two patients were treated with Tridecamine. This antihistaminic preparation was employed here as an "assist" to an elimination program based upon investigative studies. None of these patients experienced complete relief with the use of Tridecamine and the continued exposure to environmental factors. Under these conditions, results were more than adequate. Tridecamine was discontinued in two patients because of drowsiness.

Acute Upper Respiratory Infection.—Seven patients were relieved of profuse watery nasal discharge while taking Tridecamine. No effect was noted on the course, duration or severity of the infectious process.

SUMMARY

Tridecamine was used as adjunctive antihistaminic therapy in 284 patients. Over-all results were equal to or superior to those resulting from other antihistaminic preparations. Clinical response was immediate and the effect was prolonged over a twelve-hour period. The drug was discontinued in six patients because of drowsiness and in one patient because of nausea. The drowsiness was probably the result of dosage and may have been avoided with suitable adjustment.

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THE EMOTION OF CONVICTION

In the mind of a rigorously trained enquirer, the process of believing is, I apprehend, this: First comes the investigation, a set of facts are sifted and a set of arguments weighed; then the intellect perceives the result of those arguments, and, we say, assents to it. Then an emotion more or less strong sets in, which completes the whole. In calm and quiet minds, the intellectual part of this process is so much the strongest that they are hardly conscious of anything else; and as these quiet, careful people have written our treatises, we do not find it explained in them how important the emotional part is.—WALTER BAGEHOT, Literary Studies, Vol. III, 1871.

THE ACTION AND CLINICAL USE OF EPHEDRINE

An Alkaloid Isolated from the Chinese Drug Ma Huang

Historical Document

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Ma huang *(Ephedra vulgaris* var. *helvetica,* family *Gnetacaea)* has been known in Chinese medicine for some 5,100 years. It was one of the drugs tested by Emperor Shen Nung (about 3200 B.C.). The Chinese use it as a diaphoretic, circulatory stimulant, antipyretic, sedative in cough, etc., and it has been incorporated into many famous prescriptions, including one for typhoid. The plant is a low, practically leafless shrub, about 60 to 90 cm. high, which is sold freely in the vicinity of Peking. According to reports, it is indigenous to the sea coast and to the provinces of Chihli, Szechuan, Kansu, Shensi, Honan, Shantung and Kiangsu. It also grows in central Europe.

Ephedrine, the alkaloidal active principle, was first isolated in an impure form from the stems of ma huang in 1885 by G. Yamanashi, working at the Osaka Experimental Station in Japan and using the alkali-ether method. On Yamanashi's death, the study was continued and improved by Nagai, with the assistance of Y. Hori. Merck reported that he separated the same alkaloid in 1888 by the same method from the same variety of the plant. In 1923, Chen reisolated ephedrine from ma huang by the ammonia-chloroform method. The chemical structure of ephedrine has been accepted as B-phenyl-B-hydroxy-a-methyl-ethyl-methylamine.

Its synthesis has been studied by Schmidt, Nagai, and Späth and Göhring. The racemic mixture of the synthetic product has been patented by Nagai under the name of methylmydriatin in England, Canada and the United States. A review of the isolation, constitution, isomerism, properties, derivatives and synthesis of ephedrine and pseudoephedrine, with a complete bibliography, has been prepared by Chen and Kao, and will be published shortly in the *Journal of the American Pharmaceutical Association.*

PHARMACOLOGIC ACTION

The outstanding effects of ephedrine are due to the stimulation of the sympathetic nervous system and are qualitatively identical with those of

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In view of the fact that ephedrine has been used for thirty years, the tables attesting to its action and some parts of the original paper have been omitted in the interests of space.

epinephrine. As these effects are essentially the same in isolated organs or after destruction of the central nervous system, the drug acts peripherally like epinephrine, and is a true "sympathomimetic amine." In addition, it stimulates the central nervous system and depresses the heart, but these effects are ordinarily elicited only by toxic doses.

Action on the Circulation.—Rise in blood pressure following intravenous injection of ephedrine was first observed in rabbits in 1917 by Amatsu and Kubota. We demonstrated similar effects in other animals in 1924. We also found that ephedrine raises blood pressure in man when it is taken by mouth. We and also Chen and Meek showed that the rise in blood pressure produced by ephedrine is much more prolonged than is the case with epinephrine. A single intravenous injection of from 1 to 10 mg. per kilogram often raises the pressure of an anesthetized dog by 100 or more millimeters of mercury, and maintains this rise for at least fifteen to twenty-five minutes. The rise in blood pressure does not strictly depend on the quantity of ephedrine given. Equally important factors are the kind of anesthetic and the condition of the animal prior to its administration. Under phenobarbital anesthesia, the rise seems to be higher than under morphine-urethane anesthesia. With ether anesthesia a primary rise may be followed by a fall with recovery. The initial level of blood pressure has a bearing on the response. If the blood pressure is very low, there is observed a less striking rise, and sometimes the blood pressure falls even after small doses. In the decerebrated dog, the dose that ordinarily raises blood pressure may lower it. Other operative procedures, such as thoracotomy and laparotomy, may lessen its power to raise the blood pressure. By repeated intravenous injections of the same dose of 1 or more mg. per kilogram, the first one is the most effective in raising and sustaining the blood pressure. Subsequent injections become more and more ineffective not only in duration but also in the degree of pressure elevation.

The rise in blood pressure produced by ephedrine is due to simultaneous vasoconstriction and cardiac stimulation, produced by stimulation of the corresponding synthetic fibers. Vasoconstriction by ephedrine was observed by Amatsu and Kubota in perfusing the legs of frogs and isolated organs of dogs. These results were confirmed on isolated mammalian organs by us and by Chen and Meek. In plethysmographic studies, it was found that as blood pressure rises pure vasoconstriction is evident only in the splenic vessels, constriction followed by dilatation in the kidney, and usually pure dilatation in the intestinal and leg vessels. Evidently cardiac stimulation plays a larger share than vasoconstriction in the pressor effect of ephedrine in anesthetized animals.

The action of ephedrine on the mammalian heart *in situ* is essentially similar to that of stimulation of the accelerator nerve—an increase in rate and amplitude of contractions. If the vagi are intact, the heart may be

slowed reflexly as pressure rises, though amplitude of contraction is increased. After section of the vagi, or after atropine, ephedrine always accelerates the heart rate. It was found that ephedrine stimulates the stellate ganglions as well as the sympathetic endings or myoneural junctions in the heart, an action that is apparently not shared by the closely related amines epinephrine and tyramine, which stimulate only the endings or myoneural junctions.

Another important feature in the action of ephedrine on the heart is the depression. In amphibian hearts, whose sympathetic innervation is relatively unimportant, depression may be the only effect of ephedrine. Thus, Amatsu and Kubota reported that ephedrine causes depression of rate and amplitude of contractions of the frog's heart, with final diastolic arrest. Similar results were obtained by Chen and Meek with hearts of frogs and turtles. With the isolated mammalian heart it was found that while dilute solutions of ephedrine cause stimulation, stronger concentrations produce only depressions or arrest. In the intact normal animals this depressant action on the heart is not evident with small doses of ephedrine (from 1 to 10 mg. per kilogram), by which blood pressure is uniformly raised and cardiac contractions increased. Accelerator stimulation appears to overcome entirely the cardiac depressant action of ephedrine. Toxic doses (from 40 to 65 mg. per kilogram) in the anesthetized dog may lead to rapid failure of the heart, with a result of sudden fall in blood pressure. Electrocardiographic studies in dogs and rabbits show that small doses given intravenously cause nothing more than some alteration of the T-wave. Massive doses (from 40 to 75 mg. per kilogram) appear to depress the automatic and conductive system in a descending order; that is, from the sino-auricular node to the termination of the Purkinje system. This leads to bradycardia, even after atropine, prolongation of the P-R interval, partial auriculoventricular block, nodal rhythm, ventricular escape or extrasystoles, bundle-branch block, and finally ventricular fibrillation.

The effect of ephedrine on the circulatory depression produced by histamine, peptone, anaphylaxis, trauma and hemorrhage was investigated in dogs by Chen. In his experiments, ephedrine raises blood pressure in the early stage of shock and hemorrhage, but it fails to do so when the heart beat becomes impaired, or respiration ceases, or the degree of shock is too extensive, or when hemorrhage exceeds 25 per cent of the total blood volume. In some experiments (unpublished) it was found that even a small dose of ephedrine (1 mg per kilogram) might cause cardiac failure when injected after a prolonged period (thirty minutes) of low blood pressure following histamine. Apparently a heart depressed by continued low blood pressure, with consequent inadequate coronary flow, is more sensitive to the depressant action of ephedrine, and less responsive to its stimulant effect, than the normal heart.

Action on Smooth Muscle.—Ephedrine produces mydriasis when applied locally. This was first shown in 1887 by Miura, and by Takahashi and Miura in 1888. These observers found that the effect is due to the stimulation of the sympathetic system and not to the depression of the oculomotor fibers. We reached similar conclusions, finding that in ephedrine mydriasis the light reflex is retained and physostigmine causes prompt miosis, while after atropine ephedrine causes further dilatation of the pupil. We also noted that after the long ciliary nerves have degenerated, following extirpation of the superior cervical sympathetic ganglion, ephedrine causes definite dilatation of the denervated pupil. The action of ephedrine on the pupil is therefore analagous to that of epinephrine, and it is a question whether it stimulates the sympathetic endings or the myoneural junctions. Ephedrine does not irritate or injure the ocular tissues, has little apparent effect on the conjunctival blood vessels, and has no local anesthetic effect.

Bronchial muscle is relaxed by ephedrine, as by epinephrine. This was shown by Amatsu and Kubota, who found that ephedrine increases the respiratory volume of rabbits, after pilocarpine, peptone or muscarine has produced bronchial spasm. We made a similar observation on a dog rendered asthmatic by physostigmine and found ephedrine to be less effective than epinephrine.

Movements of the isolated intestines of the cat or rabbit are inhibited and the muscle is relaxed by ephedrine. This was first described by Amatsu and Kubota and confirmed by To and by us. To found that the isolated uterus of the cat or the rabbit is relaxed by small doses and is stimulated by greater concentrations, and that the inhibitory action on the intestine is 1,000 times less sensitive than that of epinephrine. Intestines in situ are also relaxed when ephedrine is injected intravenously, while the uterus is stimulated in the anesthetized dog.

Action on Secretions.—Submaxillary secretion is sometimes increased when ephedrine is injected intravenously in anesthetized dogs. The effect is not prevented by atropine and is therefore comparable to that of stimulation of the sympathetic innervation. Gastric secretion is always increased, though slightly, and other digestive secretions are not affected. Lymph flow from the thoracic duct is increased as blood pressure rises, and urine output is usually increased in dogs after the vasoconstrictor effect has disappeared. An increase in sweat secretion has not been demonstrated experimentally. In brief, the action of ephedrine on secretions is unimportant.

Toxicity.—The fatal dose of ephedrine hydrochloride, by subcutaneous injection, was found by Miura to be from 0.3 to 0.46 Gm per kilogram in rabbits, and 0.22 Gm per kilogram in dogs. In more extended experiments, Chen found that the minimum lethal dose of ephedrine sulphate,

by intravenous injection, is, in milligrams per kilogram, for white rats, from 135 to 140; for rabbits, from 66 to 70; for cats, 75, and for dogs, from 70 to 75. In rabbits by intraperitoneal injection, the lethal dose is from 310 to 400; by intramuscular injection, 340; by subcutaneous administration, from 320 to 400, and by mouth, 590. Fujii found a lethal dose of 500 mg per kilogram in mice by subcutaneous injection.

Death usually follows a period of clonic convulsions and is due primarily to acute cardiac failure. When large but sublethal doses are given repeatedly there are no symptoms, no interference with the normal gain in weight, no tolerance, and no pathologic changes in the viscera. It is clear that ephedrine is not very toxic, and the margin of safety is comfortably wide.

Mode of Action.—Most of the physiologic effects of ephedrine are referable to stimulation of the sympathetic nervous system. The fact that ephedrine produces mydriasis after the complete degeneration of the long ciliary nerves throws doubt on its stimulating strictly the sympathetic endings. It may act on the structures more peripheral to the endings (myoneural junctions). In the heart the action appears to involve sympathetic ganglions as well as the endings, or myoneural junctions, but an action on other ganglions cannot be demonstrated.

Ephedrine appears also to stimulate the central nervous system. Rabbits narcotized by chloral can be easily awakened by therapeutic doses of ephedrine, as shown by Airila and by Morita. Preliminary experiments dealing with the action of ephedrine as a respiratory stimulant in acute morphine poisoning in animals indicate that it is superior to caffeine, atrophine, strychnine, camphor or carbon dioxide inhalation. In man, moderate doses sometimes cause tremor, nausea and insomnia, which in all probability is due to the stimulation of the central nervous system.

The fact that ephedrine elicits prolonged epinephrine effects in animals suggests that it may act through stimulation of the suprarenal glands. A series of five experiments, two on cats and three on dogs whose suprarenals were tied off or removed, showed conclusively that the effects of ephedrine are not decreased by the absence of suprarenal secretion.

Comparison with Epinephrine.—Ephedrine may be looked on as a weaker epinephrine; that is, its effects are not as intense as those of epinephrine. It has a definite depressant action on the heart in large doses, or when the heart is under unfavorable conditions. From the therapeutic point of view the advantages of ephedrine over epinephrine are its much more prolonged action, its effect absorption from the intestinal tract, its easy isolation, and its stability in solutions even after boiling, or after exposure to light and air for as long as nine months. Its toxicity being low, and it being evident that no tolerance or habit is developed by its use, the drug appears to deserve clinical trials as a possible sub-

stitute for or adjuvant to epinephrine. As far as they have gone, such trials are encouraging.

CLINICAL RESULTS

As a Mydriatic.—The action of ephedrine on the human eye was studied in 1887 by Miura and in 1889 by De Vriese. They found that a 10 per cent solution of ephedrine hydrochloride causes mydriasis in from forty to sixty minutes, lasting from five to twenty hours. There is no cycloplegia, no secondary inflammation, no change in intra-ocular tension, and no untoward effects after prolonged use. We obtained similar results with a 4 per cent solution. As a result of the pioneer work of Miura, ephedrine has been advocated as a mydriatic for examination of the fundus, and is employed for this purpose often in combination with homatropine. Merck names this mixture "mydrin." The pupil returns to normal size within six hours with such a mixture. Up to the time of the work of Chen and Schmidt, no other therapeutic application was made.

As an Astringent to Mucous Membranes.—Our statement that ephedrine effects are qualitatively the same as those of epinephrine suggested to Dr. Alice H. Cook of the department of otolaryngology of the Peking Union Medical College the use of ephedrine locally in the nose and throat. She found that a 10 per cent solution of ephedrine sulphate causes almost immediate shrinkage of an engorged nasal mucous membrane, and that the action is more rapid and complete than that of a 4 per cent solution of cocaine hydrochloride. This subject was investigated more thoroughly by Fetterolf and Sponsler, who used a 5 per cent solution of ephedrine sulphate and found it so effective that they described ephedrine as a drug which, for use in the nose, "has all the advantages of epinephrine with perhaps none of its disadvantages." Shrinkage of the turbinate begins almost immediately, is complete within five minutes, and persists for nearly three hours. There is no sign of local irritation or subsequent dilatation, and by repeated administration it is possible to control the symptoms of engorgement with no untoward effects. Dunlap of Peking Union Medical College has used a 5 per cent solution with good results in acute and subacute inflammations of the nose and in vasomotor rhinitis. Middleton and Chen used a 1 per cent solution in the nose, with good results. Fahr succeeded in relieving headache due to sinusitis with the same strength of solution.

When ephedrine hydrocholoride is used, some patients complain of a "stinging" sensation, but this is not noticed with the sulphate. Growth of molds in the solution due to warm weather can be prevented by the addition of a few crystals of menthol, camphor or thymol.

The favorable results obtained with ephedrine as a local application to the nose suggests its use on other mucous membranes, particularly those

of the urinary tract. So far no reports of its use in this connection have been published.

As a Circulatory Stimulant.—(a) In the absence of circulatory depression: We showed that blood pressure of normal men can be raised by ephedrine given by mouth or by subcutaneous or intramuscular injection. Its action on the circulation was studied by Miller in a series of eighty-four patients, and by Middleton and Chen. Miller found in about 83 per cent of his cases a rise in systolic blood pressure, varying from a few millimeters of mercury to 60 or 70, while diastolic pressure is not constantly affected, though it tends to rise. The extent of the rise is as great when the drug is given by mouth as when it is injected subcutaneously, but it develops more slowly after oral administration. In 8 per cent of Miller's cases ephedrine did not change blood pressure, while in 7 per cent it was followed by a fall in pressure. When a rise in pressure occurs it usually lasts several hours, and in some cases it persists for more than twenty hours after a single dose. During the rise in pressure the pulse is usually slowed, though occasionally it is accelerated. The heart sounds are stronger, and systolic murmurs often appear at the apex or base. These murmurs were attributed to distention of the heart, and this was confirmed by fluoroscopic studies (Miller). Tonal arrhythmia is sometimes noted in taking blood pressure. Occasionally, auricular or ventricular extrasystoles are demonstrated by the electrocardiogram.

The average dose of ephedrine sulphate required to raise the blood pressure lies between 60 and 150 mg (from 1 to 2½ grains) for normal adults, given by mouth in capsule, or by hypodermic injection. As much as 400 mg (6⅔ grains) has been given in a single dose without untoward effects.

(b) In hypotension: The effect of ephedrine in chronic hypotension (systolic level below 100 millimeters of mercury) was studied by Miller in twenty-three patients. It raised the blood pressure without a single exception. Middleton and Chen obtained similar results in eight patients. It was hoped that, by repeated administration of ephedrine, blood pressure might be maintained at a normal level continuously in these cases, but this has been proved impracticable; for when a dose of ephedrine is repeated before the effects of a preceding one have worn away, the pressor effect becomes less and less marked, and it is only after an interval of about twenty-four hours or more than a second dose is as effective as the first. If the dose is increased the pressor response may or may not be greater, but these patients usually show nausea, tremor, etc., which subside only when the dose is reduced. The benefit to be expected from ephedrine in chronic hypotension is therefore only that which follows rather brief periods of elevation of blood pressure to the normal level (Miller).

Chronic hypotension is most marked in Addison's disease, and it was

hoped that ephedrine would be of value in these patients. We tried ephedrine in a single case with much benefit. A man, aged 30, Chinese, a huckster, was diagnosed as having Addison's disease, syphilitic periostitis and pulmonary tuberculosis. As a result, we felt that ephedrine might prove to be a specific in Addison's disease. Subsequent investigation shows that this is not so, for the striking improvement shown by their patient has not been manifested in any other similar cases. Thus, Miller found that while ephedrine caused temporary improvement in two cases, the effect could not be sustained and both patients died. Rowntree treated three cases with ephedrine, with improvement in two, while the third patient complained of headache after ephedrine and the drug had to be withheld. The effect of ephedrine in Addison's disease is probably analagous to its effect in simple hypotension, and only brief periods of elevation of blood pressure can be expected from it. Because of the underlying pathologic condition, Addison's disease is uniformly fatal, so that it will be absurd to hope for a cure from the use of ephedrine.

In acute circulatory crises, ephedrine would be expected to be of more value. We investigated its effect in surgical shock in a single patient, with encouraging results. Miller reported real improvement in two cases in profound shock. Since then it has been tried in a large number of cases of shock and hemorrhage, usually without beneficial result, even though the drug is given intravenously. The experiments made by Chen on the effect of ephedrine in various forms of shock in dogs indicate that the drug is useful only under suitable conditions. It is probable that the integrity of the heart function is the chief factor, for unless the heart is in good condition ephedrine may have no effect or produce simple depression. When blood pressure has been low for some time the heart function must be impaired through deficient coronary flow, and ephedrine may likely injure the heart under the circumstances that call most urgently for a circulatory stimulant. Another factor is the relative weakness of ephedrine as a stimulant to the vasoconstrictor and cardiac accelerator system, so that it may be unable to produce any effect in cases of shock and hemorrhage, in which vasoconstriction and cardiac acceleration are already present.

In Cardiac Disorders.—Miller reported the occurrence of transitory pulsus alternans in a patient with myocardial degeneration. Another patient with complete heart block showed an increase in both auricular and ventricular rates after ephedrine. Its action in auricular fibrillation was studied by Middleton and Chen in a single patient who had developed hiccup in addition to cyanosis, edema and dyspnea. Ephedrine caused a rise in arterial pressure and a fall in venous pressure, and stopped the hiccup, but had no effect on the fibrillation. It is evident that a potential cardiac depressant and an active accelerator stimulant like ephedrine must be used with caution in the presence of cardiac disease. The possibility of benefit by ephedrine

in cardiac decompensation, evident in the patient of Middleton and Chen, deserves further investigation, as well as its action in combination with digitalis.

In Asthma.—Miller found that ephedrine given by mouth or injection during attacks improved six out of seven cases of asthma. In four patients ephedrine by mouth brought complete relief; in two others it reduced markedly the number of epinephrine injections that were required, while in only one patient did it fail entirely. In a much larger series of patients he has found only exceptional instances of complete failure of ephedrine to relieve the paroxysms, though a large proportion of the patients continue to require occasional injections of epinephrine. The success of epinephrine when ephedrine alone is unable to bring complete bronchial relaxation is to be expected from our experiments, as we found that ephedrine is a weaker bronchodilator than epinephrine in animals. A curious feature in the action of ephedrine in asthmatic patients is that it usually dilates the bronchioles without raising systemic blood pressure, while a similar dose regularly raises blood pressure in nonasthmatic patients. The difference must be due to an effect on the pulmonary circulation. Middleton and Chen studied ten cases of asthma not associated with cardiac disease. Of these, six were definitely improved, two doubtful, and the other two not affected. Wearn used ephedrine in six cases of asthma due to sensitization, in several associated with chronic bronchitis, and in one with tuberculosis. Relief was brought about when given by mouth, in from 60 to 100 mg doses.

Other Effects.—Basal metabolism was found to be increased regularly after ephedrine by Miller and by Rowntree. Its effects on blood sugar were inconstant in Miller's cases, though Nagel reported a definite rise after intravenous injection in rabbits. Urine secretion was not constantly altered in Miller's series, though there was a tendency to diuresis after the drug. Miller tried ephedrine in two cases of urticaria, both of which were relieved by it. As an ingredient of local anesthetic solutions ephedrine seems to be too weak a vasoconstrictor, for it may be absorbed from the subcutaneous tissues and produce systemic effects. In one case a marked rise in blood pressure followed its use in a procaine solution, and local anesthesia was imperfect. Obviously, such a procedure is unsafe.

Untoward Effects.—No serious results have been reported from the use of ephedrine in man, even in single doses of 400 mg or in portions of 150 mg repeated every three hours day and night. No signs of habit formation or development of tolerance have been encountered, even when the drug has been given over a period of months. Some patients, especially women, after receiving 200 mg of ephedrine by mouth, complain of some of the following symptoms: perspiration, chill, palpitation, weak-

ness, dizziness, nervousness, tremor, nausea and epigastric discomfort. Sweating and tremor can be objectively confirmed. While it is interesting to note that the drug actually possesses diaphoretic properties, for which it has been highly esteemed in China, the action is apparent only in persons who show obvious signs of an effect on the central nervous system. In some patients insomnia and some of the foregoing symptoms develop after the drug has been given in smaller doses for some time (several days or weeks) and they subside when the drug is withdrawn. The most probable explanation of these effects is a stimulation of the central nervous system.

In several cases transient gross albuminuria develops after ephedrine, and in most cases it is possible by delicate tests to show the presence of some albumin in the urine after the drug. This phenomenon has been studied recently by Starr, who finds similar results from other vasoconstrictor agencies (epinephrine, asphyxia). He attributes the albuminuria wholly to renal vasoconstriction, and as none of these patients show any other signs of deranged kidney function, it is evident that ephedrine does not injure the kidney directly.

The possibility of serious depression of a weakened heart by ephedrine has been evident only in the case of myocarditis, reported by Miller, who showed an alternating pulse after the drug was given. The effect was transitory and no serious after-effects were seen. Experimental evidence indicates that ephedrine, injected intravenously in cases of profound shock of thirty minutes or more duration, may cause cardiac failure, but so far the worst effect from ephedrine in human subjects in shock has been a steady, uninterrupted progression of the condition.

It is evident, therefore, that each of the three chief features in the action of ephedrine, stimulation of the sympathetic innervation, stimulation of the central nervous system, and the depression of the heart, may produce untoward effects in human beings. Stimulation of the sympathetic fibers in the kidney may produce albuminuria, stimulation of the central nervous system may cause insomnia, nausea, tremor, etc., and depression of the heart may cause arrhythmias, or possibly even cardiac failure, though so far this has not been reported.

COMMENT

The use of ephedrine as a substitute for epinephrine in therapeutics is based on the fact that the substances are closely related chemically and physiologically. Ephedrine, while less active physiologically, has the advantage over epinephrine of eliciting more prolonged effects, of being effectively absorbed when taken by mouth, and of being a much more stable substance. Its low toxicity and its occurrence in a common Chinese plant are circumstances favorable to its widespread use, should it be found of value clinically.

The results of clinical trials of ephedrine so far indicate that it will

be found to be most useful as a local application to the nose in cases of chronic congestive conditions such as hypertrophic rhinitis and hay fever. This alone would make it a useful drug.

Of almost equal promise are its effects in asthma. A drug which will control the symptoms entirely, or at least reduce the number of epinephrine injections that are required, and which can be given effectively by mouth, appears to be a real addition to therapeutics. The precise limitations of ephedrine in asthma are not yet evident, but it seems certain that it will be found useful in many, if not in most, cases.

As a circulatory stimulant, ephedrine has been rather a disappointment. In chronic hypotension it seems to be of little or no value, and in acute circulatory crises it usually fails to work. It is possible that ephedrine will find a place in the treatment of acute crises when the reasons for its usual lack of effect are considered. These are its inability to cause appreciable stimulation of the vasomotor system because it is a weak stimulant and the system is probably already stimulated, and its tendency to depress the heart. If ephedrine is given with epinephrine, ephedrine may prolong the effect of the stronger stimulant. The tendency to cardiac depression can be minimized by improving the coronary circulation by means of epinephrine and saline infusion or transfusion of blood before ephedrine is given. It should be possible, by means of a combination of ephedrine with preliminary infusion of fluid and epinephrine, to secure some beneficial effects from ephedrine in many cases of shock. Ephedrine should not be injected intravenously in cases of profound shock if epinephrine fails to elicit a response, for it can do no good and may do harm. Ephedrine is certainly not to be regarded as a specific for shock. Its actual usefulness remains to be determined clinically.

Ephedrine may prove valuable in the treatment of anaphylaxis and urticaria, and as a respiratory stimulant in poisoning by narcotic drugs. In the latter connection it seems to be more regularly effective and less dangerous than any other single drug in experimental morphine poisoning. Its use in ophthalmoscopic examination should not be lost sight of.

All of the results reported above have been obtained with ephedrine sulphate or hydrochloride, salts of the alkaloid of the Chinese plant ma huang. There are other alkaloids, isomeric with ephedrine (pseudoephedrine, methylmydriatine) which may differ physiologically. Until a comparative study of these compounds is carefully made, the statements mentioned above can be applied only to ephedrine, obtained from the Chinese plant by the methods already described.

ABSTRACT OF DISCUSSION

Dr. George E. Brown, Rochester, Minnesota: Through the courtesy of Dr. Bernard Read of Peking, we were furnished with an amount of this drug for clinical trial, and Dr. Rowntree and I were particularly interested

in determining its efficacy in Addison's disease. We observed fourteen cases of Addison's disease last year which were treated with ephedrine. There is no question as to the efficacy of this drug in increasing the blood pressure. We were able to demonstrate increases of from 25 to 30 mm of mercury. This increase in blood pressure was not accompanied with the desired systemic improvement that we had anticipated; that is, one could obtain a rise in blood pressure, but the patient did not accordingly feel improved in his clinical condition. We tried this drug in three cases of Addison's disease in the so-called shock state but were unable to demonstrate any particular benefit in this condition. In cases of essential hypotension and chronic exhaustion, we could also demonstrate a very definite increase in blood pressure from doses of 100 to 150 mg a day. One patient had 150 mg a day for thirty days and a very definitely maintained increase in his systolic pressure, but without a significant change in the diastolic pressure. There was usually some subjective improvement. Toxic effects were lacking or very mild. There is no question as to the pressor effects of this drug. Raising the blood pressure would not, of course, affect the underlying disease. Dr. Gaarde of the Mayo Clinic has been using ephedrine in ragweed hay fever and he reports that 50 per cent of the patients had marked relief for from three to eight hours. To me, it is a most interesting idea that a drug known in Chinese medicine for 5,000 years is now shown to have pharmacologic action similar to epinephrine and promises to play a role in our future treatment of disease.

Dr. A. P. Munsch, St. Louis: I should like to ask Dr. Chen if it has been observed whether the blood sugar is increased when this drug is used. In cases of diabetes mellitus with low blood pressure, would this drug be available and effective or would it be a danger to the patient?

Dr. Ralph H. Major, Kansas City, Missouri: We have worked with this drug in the laboratory and can confirm the rise in blood pressure which Dr. Chen described. I have seen a marked improvement in asthmatic patients and have also been able to raise the blood pressure in patients suffering from hypotension. It is a very interesting feature that the action of ephedrine is similar to that of epinephrine, but it can be administered by mouth. I am sure that patients will appreciate this feature. I should like to know whether Dr. Chen has found it necessary to give patients with hypotension constantly increasing doses in order to raise their blood pressure; also whether he has studied microscopically the arterial or capillary changes produced by this drug.

Dr. Joseph L. Miller, Chicago: Does this drug relieve bronchial asthma and hay fever when taken by mouth or must it be given subcutaneously?

We are much in need of a drug which will relieve asthma that can be taken orally.

Dr. Clyde Brooks, Tuscaloosa, Alabama: I should like to ask Dr. Chen whether this drug acts quantitatively and qualitatively like epinephrine on all the tissues and organs which he has tested; in other words, whether it has what is termed a sympathomimetic action. Another point is, whereas in Dr. Chen's tracings there is a rise in blood pressure which lasts for a long time, the volume curve at first shows decrease followed by increase in volume. Why does the volume curve not follow the blood pressure curve? Where does the blood go during the decrease, and where does it come from during the increase in volume?

Dr. J. I. Johnston, Pittsburgh: Answering Dr. Miller's question, the drug certainly seems to take the place of epinephrine in relieving bronchial asthma. It has been particularly useful in cases in which pulmonary emphysema was present and the patients have been advanced in years. Our experience seems to bear out all Dr. Chen has said. We have, however, seen one drawback and this has been explained in the paper. Our patients complained of sleeplessness. The drug relieved the syndrome of asthma, it produced a definite rise in blood pressure, and the only objection seen was the inability to sleep well.

Dr. Julian E. Benjamin, Cincinnati: Will Dr. Chen tell whether he has observed the effect of ephedrine in collapse in pneumonia? Would he also explain whether the action of the drug in stimulating the human heart is similar to the experiment shown here, namely, that in the initial phase there is stimulation followed by depression. Is this true when the drug is given by mouth? Is there diminished kidney excretion when the drug is given clinically by mouth as when it is given intravenously in the experiment?

Dr. K. K. Chen, Madison, Wisconsin: An English drug house recently sold to this country a considerable quantity of so-called ephedrine hydrochloride. We found that the drug was not effective clinically in the control of asthma, and that its physical constants were entirely different from those of our own product. I hope that any who use ephedrine will be certain of its purity in order to avoid any unnecessary discrepancy of results which may soon appear in literature. In answer to Dr. Munsch's question, Dr. T. G. Miller's clinical work does not indicate any consistent change of blood sugar after the administration of ephedrine. In our experiments with animals (rabbits and dogs), we have found hyperglycemia which is not so high as occurs after ordinary doses of epinephrine. I cannot tell whether it will be dangerous in diabetes or not. The question can be answered only by trial. At the Wisconsin General Hospital we

gave ephedrine to a diabetic patient because of hypotension. No untoward symptoms were experienced by that patient although there was a slight disturbance of blood sugar. With regard to Dr. Major's questions, the most effective dose is the first one; for repeated administration may not raise as much blood pressure as the first. I do not believe there is any good reason to increase the dose. It is usually often enough if the drug is given two or three times a day. Concerning the action of ephedrine on capillaries, I have done some work on the frog's kidney and tongue. The results so far are not definite and I am not in position to make any statement. Dr. Miller's question has been answered by Dr. Johnston. Ephedrine can be taken by mouth instead of by hypodermic injection. The effect is just the same. In hay fever we have not enough data to justify a conclusion. In our experience, when there is no asthmatic attack in association with it, the local application of ephedrine to the nasal mucosa markedly relieves the congestion. Anyway, I do not think that ephedrine can desensitize the patient, because there is no ground for it. Answering Dr. Brooks' question, roughly speaking, ephedrine acts like epinephrine. In a limited period of time, I cannot enumerate the exceptions, such as the action of ephedrine on the stellate ganglions, which is not shared by epinephrine. When injected intravenously, the intestinal and leg vessels are dilated, while the splenic and renal vessels are constricted. The distribution of blood in the body is therefore obvious. Dr. Johnston's remarks need no answer, with the possible exception of the sleeplessness. I do not know how many cases he has treated. In our experience, as in Dr. Miller's, sleeplessness is not a constant feature. The more common complaints are perspiration and tremor. At the Wisconsin General Hospital we have treated ten cases of asthma to date. None of them showed insomnia. One patient with simple chronic hypotension was troubled with sleeplessness, but we were able to control it by the administration of barbital. Dr. Benjamin mentioned the possibility of giving ephedrine in the collapse of pneumonia. We have not enough data on that subject. We had, however, a very interesting case at Philadelphia. A resident came down with pneumonia. He was on the verge of death and became nearly breathless. Ephedrine was administered intramuscularly twice. Within a few hours his condition was much improved, and he recovered in a few days. We do not know whether it was a spontaneous recovery or whether ephedrine actually helped him to overcome the crisis. It certainly gives us a favorable hint. Dr. Benjamin also asked whether there is any renal vasoconstriction after the use of ephedrine in human beings. I think there is. Dr. Starr has published his results recently. He found a transient albuminuria after ephedrine, which he attributes to renal vasoconstriction.

Editorial

The opinions expressed by the writers of editorials in the ANNALS *do not necessarily represent the group opinion of the Board or of the College.*

THE WHITE HOUSE CONFERENCE ON CHILDREN AND YOUTH

Next year will see the convening in Washington of the decennial White House Conference on Children and Youth, called "to promote opportunities for children and youth to realize their full potential for a creative life." This will be the sixth such conference, the first having been held under the auspices of Theodore Roosevelt in 1909. Each of the meetings in the past has sparked significant and far-reaching advances in medical treatment, education, social services, and teaching of normal as well as handicapped and underprivileged children. It can be expected that the Conference of 1960, preparations for which are already well underway, will prove to be no exception.

The 1960 Conference presents a unique opportunity to those physicians and lay persons interested in furthering the cause of allergy and its treatment. The public is familiar with such terms as asthma, eczema, hay fever, and hives, but relatively few are aware that these are merely different manifestations of the protean disease state called *allergy*. Still fewer realize that, left untreated, allergy tends to become chronic and intractable. We need call to mind the tragic picture of only one crippled asthmatic child to appreciate the full import of allergy recognized or treated too late.

It has been reliably estimated that some 20 per cent of the children in America will be seriously affected by some form of allergy before they reach the age of fifteen. Yet the subject of "Pediatric Allergy" has never yet been placed on the agenda of a White House Conference—thus the unique opportunity available to us this year.

Probably the most important result of a White House discussion of the allergic child would be a dramatic increase in public recognition and understanding of the disease. Since as much as 80 per cent of all recognized allergy makes its first appearance in childhood, increased awareness on the part of the public cannot help but lead to earlier identification and more efficient treatment of the disease when it is still most amenable to therapy.

Along with increased awareness, we could expect the White House Conference to give added impetus to research into the causes and treatment of allergy. Although significant and gratifying progress has been made in recent years, there is much that remains to be clarified. Specifically, research must be done in the following areas:

1. The effects of allergy in children who, although physically below par because of their allergy, do not come under skilled medical attention.

2. The extent and degree of deprivation suffered by allergic children—scholastically and socially as well as physically.

3. Accurate statistics on mortality resulting either directly or indirectly from severe allergic illness.

4. The physical and emotional impact on the family of the allergic individual.

5. The cause and nature of special sensitivities to allergic illness, and what can be done to mitigate them.

6. Specific methods of treating allergy; for progress thus far, while significant, is far from adequate, particularly when compared with recent advances in chemotherapy or in the treatment of mental illness with drugs.

7. Planning a complete program of care for the allergic child, including special educational facilities and techniques and individualized vocational training, when needed, as well as early diagnosis and skilled treatment of the disease itself.

But a *complete* program aimed at achieving ultimate control over allergy must have *total* public support, and it is in this area that the White House Conference could play a decisive part. Special training facilities to orient doctors, nurses, and teachers to the insidious nature of allergy and to the skills required to treat it must be set up. Although government agencies and some pharmaceutical manufacturerers have been quick to support such endeavors, it is the general public which must ultimately bear the burden if a *complete* and *effective* program is to be implemented.

In the final analysis, we need a sustained effort directed toward the dissemination of information on the subject of allergic illness to the general public, in order to obtain a generous measure of public participation in a program to combat and ultimately to defeat allergic disease. Placing the subject of "The Allergic Child" on the agenda of the 1960 White House Conference could—indeed, very likely would—be the critical turning point in such an effort. It is our fervent hope that those in Washington who have been charged with determining the nature and content of the forthcoming Conference will not neglect this opportunity to strike a decisive blow against this many-faceted illness which continues to threaten the health and lives of so many of our children.

H.G.R.

INTERNATIONAL SEMINAR

The First International Seminar on the Single Annual Injection with Emulsified Extract for Allergic Disorders will be held on October 24 and 25 from 9 a.m. to 12 noon and from 2 to 5 p.m. at 75 Bay State Road, Boston, Massachusetts. All physicians who are members of The American College of Allergists are invited, although attendance will be limited, for reasons of space, to seventy-five participants. A letter of intention should be sent to Dr. Ethan Allan Brown at the earliest convenient date.

The first session will be devoted to the preparation of emulsions, their testing and administration, and the second session to informal talks by participants in the program. Sunday morning will be given over to questions and answers. There will be a cocktail party on Sunday afternoon. There is no registration fee.

The nearest hotels are the Hotel Kenmore (Kenmore Square), the Somerset Hotel (Commonwealth Avenue), and the Statler Hilton (Park Square).

Papers of Interest

Wirth, L.: Use of chlorpromazine in cough, with particular reference to whooping cough. Military Med., 122:195 (Mar.) 1958.
In 30 pertussis patients treated with chlorpromazine therapy, cough was mild and useful. In the majority of 90 other children and adults, cough of varied origin was similarly controlled.

Shick, R. M.: Periarteritis nodosa and temporal arteritis. Minnesota Med., 41:231 (Apr.) 1958.
Cortisone and corticotropin may induce remissions in periarteritis nodosa. In the treatment of temporal arteritis they may safeguard vision.

Albert, S. M., and Rechtman, A.: Serum neuropathy following routine use of tetanus antitoxin. Am. Practitioner, 9:1249 (Aug.) 1958.
Routine prophylaxis by tetanus toxoid immunization is stressed.

Tarpinian, D., Kashtan, H., and Jablokow, V.: Thrombotic thrombocytopenic purpura: report of two cases. Harper Hosp. Bull., 16:166 (July-Aug.) 1958.
Reactions are described as possibly hyperergic.

Kalz, F.: The effects of triamcinolone (aristocort) and 6-methylprednisolone (medrol) on some skin diseases. A therapeutic note. Canad. M.A.J., 79:400, (Sept. 1) 1958.
Triamcinolone rapidly controls the inflammatory phase of skin disorders with low effective maintenance dose but high incidence of minor side effects. Medrol is less potent but produces fewer side effects.

Hurst, V., and Grossman, M.: Antibiotic resistant staphylococci. Familial infections caused by exposure of babies in hospital nurseries. California J. Med., 89:107 (Aug.) 1958.
Members of two families were infected with the strain. In one, infection developed in 6 of 7 members within 8 months of the infant's arrival, and half of the other family had recurrent infections during a 13-month period. Chlormycetin is mentioned.

Dreyfuss, F.; Klein, H., and Winnik, H. Z.: The prevention of Chlorpro-Jaundice. Acta. med. orient., 16:251-254 (Nov.-Dec.) 1957.
Liver damage as resulting from Chlorpromazine can be reduced if 2 liters of sweetened tea or plain water are added to the regular daily fluid intake.

Zimmerman, Murray C.: Penicillinase-proved allergy to penicillin in poliomyelitis vaccine. J.A.M.A., 167:1807-1809 (Aug.) 1958.
Six reactions in patients given injections of poliomyelitis vaccine were considered to be due to penicillin because each patient had had a previous similar reaction known to be due to the drug; the reaction after use of the vaccine duplicated the previous penicillin reactions and each patient recovered after an injection of penicillinase.

Singer, Ellis P.: Diagnosis and therapy of hyperventilation. Mod. Med. page 81-82 (Sept.) 1958.
Diagnosis is based on cold, clammy hands, axillary sweating, dilated pupils, tachycardia, tremor and sighing respirations and confirmed by a hyperventilation test.

Bell, B., Irons, G., Jr., and Furst, W.: Prolonged urticaria after ingestion of sulfamethoxypridazine. New England J. Med., 259:585 (Sept. 18) 1958.
Following ingestion of one 0.5 g. tablet of sulfamethopyridazine (Kynex) urticaria lasted for seventeen weeks.

Kraepelien, S., Engstrom, I., and Karlberg, P.: Respiratory studies in children. II. Lung volumes in symptom-free asthmatic children, 6-14 years of age. Acta Paediat., 47:399-411 (July) 1958.
Lung volume relationships in 98 asthmatic children (66 boys, 32 girls) 6-14

years of age were studied during asymptomatic intervals and classified in three groups according to frequency of asthmatic attacks. Increasing the accuracy of clinical classification by considering frequency of attack and duration of disease is discussed.

Fang, Y.: Peripheral gangrene and hemorrhagic purpura due to penicillin sensitivity. Report of a fatal case. Chinese M. J., 76:599-601 (June) 1958.
A case of peripheral gangrene and hemorrhagic purpura due to penicillin sensitivity is reported. Clinical features, prognosis and treatment are briefly discussed.

Sherman, S., Bauer, E., Klahre, H., and Lever, P. G.: Agranulocytosis after 10 (n-methyl-piperdyl-3-methyl) phenothiazine, with recovery. New England J. Med., 258:6 (Feb. 6) 1958.
Agranulocytosis usually occurs in women within six weeks of treatment. Authors advice refraining from administering barbiturates and these tranquilizers at the same time.

Hoff, H. R.: The Hamman-Rich syndrome. Review of the literature and report of a case treated with prednisone. New England J. Med., 259:2 (July 10) 1958.
A case of five years' duration is presented. No improvement occurred after one year of treatment with prednisone.

McFarland, R. B.: Reactions to benzathine penicillin. New England J. Med., 259:2 (July 10) 1958.
Antihistamine therapy appeared to have a slight effect in diminishing the length of illness caused by allergy to benzathine penicillin.

Keil, H.: The prophylactic treatment of poison ivy dermatitis with 3-n-pentadecyl catechol using the wheal method. New York J. Med., 58:57-59 (Jan. 15) 1958.
Clinical evidence in 26 of 28 patients supports the view that the wheal method of prophylaxis with synthetic 3-n-pentadecyl catechol produces clinical hyposensitization.

Scherrer, M.: Deep-seated pulmonary infection in chronic asthmatic bronchitis. Schweiz. med. Wchnschr., 88:806 (Aug. 16) 1958.
Fifty-three per cent of 56 cases of "uncomplicated" bronchial asthma and 80 per cent of 25 patients with asthma and secondary right heart failure frequently have bronchial infection. Therapy with Chloromycetin or large doses of penicillin is indicated.

Sturmer, F. C., Jr.: Antihistamines and diphenylhydantoin-induced gingival hyperplasia. New England J. Med., 259:485 (Sept. 4) 1958.
In 28 patients with gingival hyperplasia thought to be secondary to administration of diphenylhydrantoin sodium, no improvement was noted after three months of antihistamine therapy.

Calvert, R. J., Hurworth, E., and MacBean, A. L.: Megaloblastic anemia from methophenobarbital. Blood, 13:894 (Sept.) 1958.
Methophenobarbital, taken for 8 years as an anticonvulsant appears to have caused anemia, possibly conditioned by a folic-acid-poor diet. Hematologic remission followed administration of folic acid.

Garbe, W.: The action of thenalidine tartrate (sandostene) in atopic dermatitis. Evaluation of a new antiallergic preparation for control of pruritus and treatment of various allergic dermatoses. Canad. M.A.J., 79:378 (Sept. 1) 1958.
Thenaldine tartrate, a new antiallergic with antihistamine and antipermeability action, proved effective in a majority of allergic dermatoses, with especially prompt relief of pruritus.

Mescon, H.: Eczematous hand eruptions: etiology and treatment. M. Clin. North America. p. 1361 (Sept.) 1958.
Interrelationship between psychogenic factors, bacterial and fungus infection, primary irritants, and local or systemic allergic factors must always be considered.

News Items

THE AMERICAN COLLEGE OF ALLERGISTS, INC.

Sixteenth Graduate Instructional Course and Annual Congress

February 28 - March 5, 1960

The Americana

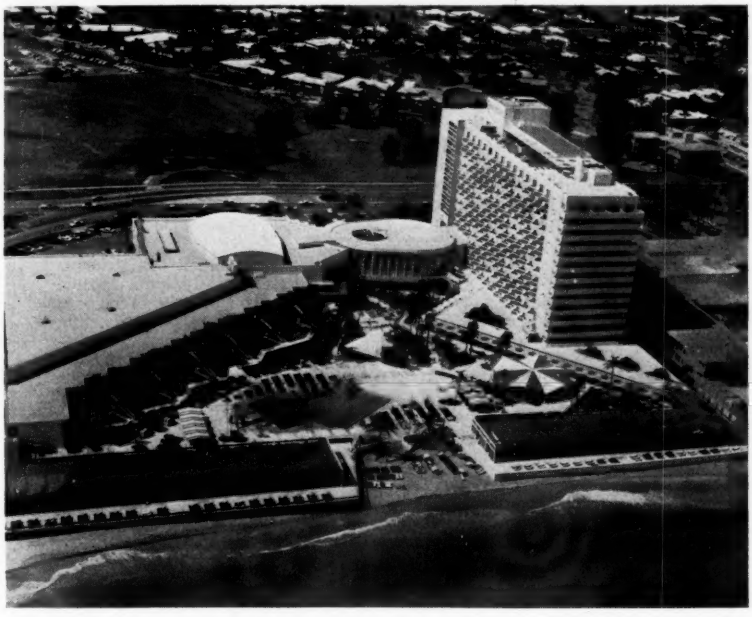
Bal Harbor, Miami Beach, Florida

The Sixteenth Annual Graduate Instructional Course and Scientific Congress of The American College of Allergists will be held at the Americana Hotel, placed in the Bal Harbor section of Miami Beach.

The Americana, one of the nation's leading resort hotels, is also famous for its ultra-modern facilities and incomparable staff of vacation and convention experts. It is a city within itself. The 30-million-dollar hotel is famous for its 780 spacious guest rooms. The Lanai Suites, which are separate from the hotel itself, are the ultimate in luxury, and are arranged on ground and first-floor plans, with openings both onto the recreation area, and a corridor leading to the hotel itself, as well as to the area given over to the exhibitions and the meetings.

There are 10 acres of ocean front, and 600 feet of private beach.

The Americana's nightclub, the Bal Masque, presents top entertainment. There



Oceanside view of the Americana, with the hotel itself at the right. To the left is the lobby, and progressing from right to left, the exhibition and convention area, and the Lanai Suites. The glass-enclosed pool is at the lower right, and the open pool at the lower left. The cabanas face either the ocean or the recreation area.

are three other dining rooms. The Gaucho Room has successively for many years won the Holiday Magazine award for its superb food.

The cabana and recreation facilities border the two outdoor swimming pools, one of which is glass-enclosed.

Here is tropical living at its very best. And, as to weather, March is undoubtedly the best month of the year for a meeting or a vacation or both, because the temperature averages 70°. Your Board of Regents chose its date on the basis that the weather in December and January is not usually dependable.

The hotel management has not only arranged for postseasonal rates for the attending physicians and their families, but will also give those who wish to spend time at the Americana either before or after the Sixteenth Annual Postgraduate Course and Congress the same low-cost "package deal." In other words it will not be necessary to mortgage either the house or the car.

For those who wish to drive, there is a five-story enclosed garage which will accommodate 200 automobiles. Above this, there is now being built 180 new deluxe guest rooms, extending from the sixth to the twelfth floor. High-speed elevators will carry physicians directly to their rooms.

The auditorium and exhibit hall will seat 5000, and is the largest privately-owned facility of its type in the country. The lighting and the acoustics are the best available.

The sooner you make your reservations, the better choice of rooms you will have.

PROMOTION TO ACTIVE FELLOWSHIP

All applications for promotion to Active Fellowship in The American College of Allergists must be completed and returned to the Treasurer, Dr. John D. Gillaspie, 2049 Broadway, Boulder, Colorado, on or before November 30, 1959, in order to be considered for promotion at the Annual Meeting in Miami Beach, Florida, February 28 to March 4, 1960.

AMERICAN COLLEGE OF CHEST PHYSICIANS

At the 25th Annual Meeting of the American College of Chest Physicians held at the Ambassador Hotel, Atlantic City, New Jersey, June 3-7, 1959, there were elected for the year 1959-1960:

President.....Seymour M. Farber, M.D., San Francisco, California
President-Elect.....M. Jay Flipse, M.D., Miami, Florida
First Vice President.....Hollis E. Johnson, M.D., Nashville, Tennessee
Second Vice President.....John F. Briggs, M.D., St. Paul, Minnesota

CANADIAN ACADEMY OF ALLERGY

The Canadian Academy of Allergy elected the following officers at a recent meeting:

President.....J. D. L. Fitzgerald, M.D.
Vice President.....C. H. A. Walton, M.D.
Secretary-Treasurer.....Jacques Leger, M.D.

CHICAGO SOCIETY OF ALLERGY

At a recent meeting of the Chicago Society of Allergy, the following were elected officers for 1959-1960:

President.....I. A. Fond, M.D., Chicago
President-Elect.....Bert B. Schoenkerman, M.D., Milwaukee
Secretary-Treasurer.....Charles M. Jenkins, M.D., Chicago

CUBAN SOCIETY OF ALLERGY

Newly elected officers of the Cuban Society of Allergy are as follows:

President.....Dr. Julio de Los Santos
Vice President.....Dr. Jose Pedrera
Secretary.....Dr. Javier Fernandez Castro
Treasurer.....Dr. Francisco de la Torre Madrazo

LOS ANGELES SOCIETY OF ALLERGY

At a meeting of the Los Angeles Society of Allergy on January 20, 1959, the following officers were elected:

Ralph Bookman, M.D., President
Isadore Pitesky, M.D., Vice President
Catherine G. Pearson, M.D., Secretary-Treasurer

NEW JERSEY ALLERGY SOCIETY

The New Jersey Allergy Society has announced the election of the following officers:

President.....Frank L. Rosen, M.D., Newark
Vice-President.....Joseph R. Jehl, M.D., Clifton
Secretary.....Herbert W. Diefendorf, M.D., Summit
Treasurer.....Francis A. Pflum, M.D., Asbury Park

SIXTEENTH ANNUAL GRADUATE INSTRUCTIONAL COURSE AND SCIENTIFIC SESSION

For the Sixteenth Annual Graduate Instructional Course and Scientific Session of The American College of Allergists to be held from February 28 to March 5, 1960, at the Americana Hotel, Bal Harbour, Miami Beach, Florida, Dr. Giles A. Koelsche of the Mayo Clinic is the Over-all Chairman. Fellows who wish to present papers at the scientific session should submit abstracts, in triplicate, to Dr. Koelsche at the Mayo Clinic, Rochester, Minnesota, at the earliest opportunity and, if possible, before the deadline of October 15, 1959. This date has been set because the complete and detailed program will once again be published in the November-December issue of the ANNALS OF ALLERGY.

Associate Fellows should also submit summaries of the papers they plan to present to Dr. Giles A. Koelsche. These should be at least 250 words in length, and the final presentation will again be eligible for the Bela Schick Prize awarded by the Women's Auxiliary of The American College of Allergists.

Students or interns who are working on any phase of allergy should be encouraged to submit papers for consideration for the Clemens von Pirquet Award, also presented by the Women's Auxiliary.

All abstracts should be submitted with pertinent data as to the author's name as he wishes it to appear in the final program, with one or, at the most, two affiliations.

Because of the attractive facilities, the reasonable rates, and the ideal date of the meeting, a record attendance is expected. Abstracts should therefore be submitted before the deadline date. Reservations at the hotel should be made as soon as attending physicians are certain of their plans. The "package deal," as it is termed, means that the room rate includes all meals at any one of the fine restaurants at the Americana, and in addition, the banquet. The same rates will be extended by the hotel management for as early before the meeting and as long after the meeting as those attending the meeting wish to stay. Members of the physicians' families are included in the arrangements. There is transportation available, without charge, to the shopping centers in Miami. All of the facilities of the fabulous Americana are similarly available to all physicians and their guests who attend the Postgraduate Course or the Scientific Session, or both.

BOOK REVIEWS

YEAR BOOK OF DERMATOLOGY AND SYPHILOLOGY, 1957-1958 SERIES. Rudolf L. Baer, M.D., Victor H. Witten, M.D. 492 pages, including indices. Chicago: Year Book Publishers, Inc., 1957. Price: $8.00.

Of the 492 pages of this issue of a series of year books distinguished for their completeness and erudition, 158 are given to Allergic Eczematous Contact; Eczematous, and Atopic Dermatidites, Urticaria, and Drug Eruptions. The remainder of the book deals with Miscellaneous Dermatoses, Cancers, Fungus, and other infections and Venereal Diseases and their treatment. A chapter is given to Investigative Studies.

Listed are the 800 or more substances and categories of contactants used for patch testing, giving the solvent and concentration to be used for each. This alone is worth the price of the book. The editorial comments which follow almost all the abstracts are, as usual, sage and lucid. The index is detailed and exact.

The book could be improved if a list of the journals from which papers had been abstracted were added to the index to authors.

An excellent work to own and to refer to often.

MOULD FUNGI AND BRONCHIAL ASTHMA. I. By P. J. Van der Werff. 174 pages, 69 photographs arranged in appendix. Leiden, the Netherlands: H. E. Stenfert Kroese, N. V.; Springfield, Illinois: Charles C Thomas, 1958. Price, $7.50.

In this short and very well written book, Doctor Van der Werff has drawn upon a wealth of experience gained in the laboratory and clinical practice with his father-in-law, the late Dr. William Kremer, who earlier had been a student and co-worker with Storm van Leeuwen, the father of mold allergy. The author has also enjoyed another unusual and fortunate association with an outstanding expert on fungi, Prof. Dr. Johanna Westerdijk of the mold culture laboratory in Baarn. Doctor Van der Werff's background, then, including proficiency in mycological techniques, as well as a broad knowledge of clinical allergy, well fits him to write authoritatively and to report his own observations as well as edit the work of others in the field of mold allergy.

The book contains only five chapters, with foreword by Professor Westerdijk, a tabulation of contents by chapters, a list of graphs and tables, and an appendix of sixty-nine plates, mostly photomicrographs. Beginning with a general consideration of climate and fungus allergy, the first chapter contains extensive bibliographic data. Then follows a brief discussion of mycology, including detailed comments on culture media and mold survey techniques. The remaining chapters deal with molds encountered in outside air and with those species and genera occurring in local environments and workshops. In respect to locally encountered molds, the author emphasizes particularly the association of molds and various types of dust. On every topic, Doctor Van der Werff first summarizes the literature then modestly adds his own observations.

Clinical considerations are conspicuous by their paucity in this first volume, but will doubtless receive more attention in Volume II.

For anyone interested in mold allergy, this book will offer very rewarding study. The bibliography alone is worth the price of the book; it is the most extensive this reviewer has seen.

H.E.P.

1958-59 YEAR BOOK OF DRUG THERAPY. Ed. by Harry Beckman. 569 pages. Chicago, Ill.: The Year Book Publishers, Inc., 1959. Price $7.50.

For less than the cost of two cents each ($7.50), the purchaser of the Year Book of Drug Therapy can obtain abstracts grouped and commented upon editorially as taken from 493 articles from 108 journals emanating from 23 countries. Twenty pages are given to the lead subject, allergy, and twelve to bronchopulmonary disorders. Approximately 90 and 100 pages are respectively given to drug treatment of cardiovascular diseases and those due to infections.

The book is well balanced and as usual represents a bird's eye view of its field. Important adverse reactions are adequately covered.

The reviewer was not only unable to discover any important contribution which had been omitted, but actually, although he routinely checks Current Contents, found a number of reports he had missed. Worth getting year after year after year.

CURRENT THERAPY, 1959. Ed. by Howard F. Conn, M.D. 730 pages. Philadelphia: W. B. Saunders Company, 1959. Price $12.00.

The "most popular compendium of treatment ever published" is here again, for 1959. Each year has seen improvements in what seemed editorial perfection.

The rotation of topics among different authors makes certain that each school of thought, when several exist, is represented. When major differences of opinion have not been reconciled, more than one method of treatment is outlined. During the last decade, every new contributor has lent authority to the successive texts and the high quality of lucid, clipped prose has been maintained.

For 1959, the inside front and back covers put within easy reach the tables of Normal Laboratory Values of Clinical Importance. A Roster of Drugs gives Trade Name, generic name, manufacturer, and package information of all medications mentioned in the text. All are again referred to for a third time, in the general Index. Shirley and Barber have prepared a comprehensive Table of Pediatric Dosages. There is a Nomogram for estimating surface area as prepared from the data of Boyd and West. The tables for making weight in volume and weight in weight percentage solutions will not be used daily, but when needed are available.

Included also are the types of treatments needed for 130 specific poisonous substances, as well as a list of the poisonous ingredients present in 48 household items, and a number of commercial products listed alphabetically from Absorbine, Jr. (thymol, iodide, and menthol), to Zotox (arsenic), with references to the appropriate paragraph in the Section on Miscellaneous Poisonings.

A book it is better to own than to wish you had.

OCCUPATIONAL ALLERGY. Lectures held during a course on Occupational Allergy organized under the auspices of the European Academy of Allergy, The Hague, May 1958. Springfield, Illinois: Charles C Thomas, 1958. Price, $10.00.

During May, 1958, the Netherlands Society of Allergy under the auspices of the European Academy of Allergy held a Congress concerned with Occupational Allergy. The proceedings are now available in English and, excepting for some non-idiomatic phrases and occasional misspellings, the thirty-seven papers presented make excellent reading.

In his Foreword, D. A. Williams says, "Of recent years there has come a growing realization of the need for a careful assessment of the role of allergy in different occupations, for the views of an authoritative group rather than that of individuals. There is still a need for brilliant individualists, but there is also a need for an amalgamation of the knowledge of allergists and of industrial medical officers."

Dr. W. Jadassohn in his Introduction notes, "In the medical world, some consider allergy as a medical specialty, such as ophthalmology, dermatology, pediatrics, etc., while for others it is a horizontal branch of medicine, 'ein Querschnittsfach' (Loeffler), meaning that of the various specialties each requires a knowledge of certain aspects of the field of allergy. I do not believe that there is a single clinical specialty where one is not called upon to resolve allergy problems or at least to consider them. The dermatologist, and I can take my own case as an example, has a daily need of a familiarity with allergy problems."

He goes on to say, "In my opinion it is quite justified that in our allergy association meetings there are always present specialists in very different branches of medicine who are particularly interested in problems of allergy. The professional allergist undoubtedly sees his problems from a point of view different than do other specialists interested in allergy. Cooperation is necessary so as to avoid as much as possible what is termed in German 'Einseitigkeit' ('onesidedness')."

The North American reader will find in these pages not a one-sidedness, but a point of view similar to but not exactly matching that of his own experience. Here are available papers on Kapok allergy, on allergy to oil of turpentine, to pharmaceuticals, to textiles, especially wool and printed cotton, to newsprint, to coffee vapors, to tobacco, to bakery products, and to exotic woods. Respiratory allergy of the medical profession is given special treatment, as is allergy in nurses and therapists.

Perhaps the treatment of penicillin sensitivity as outlined by Nilzen should more frequently be used. Certainly we do not routinely test for or treat with human dander. Someone should soon repeat Voorhorst's work in autogenous sensitivity of the atopic type to one's own dander, and confirm that the clinical results obtained are truly specific, especially in the patients employed as hairdressers. In these provocative tests to human dander reinvoked rhinitis and asthma occurred. No other sensitivity was present, and the patients responded to treatment with solutions of human dander.

Williams says of the book that it . . . "may or may not achieve finality, but if the views of some can stimulate others to more effective solution of their problems, much will have been accomplished."

WANTED—Associate, male or female, who would be interested in field of allergy—full time or part time. Will receive excellent training in allergy and internal medicine. Salary commensurate with ability and experience. Address A-10, care ANNALS OF ALLERGY.